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ORIGINAL ARTICLES

CORONARY ARTERIAL CALCIFICATION A REVIEW*

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To evaluate patients with coronary heart disease, electrocardiography can be used to learn if myocardial ischemia occurs and to evaluate its severity. If this information could be correlated with knowledge as to the cause of ischemia, understanding of these patients would be much more complete. In particular, there is need for techniques which can furnish information regarding the nature and distribution of the atherosclerotic process in the coronary arteries. To this end, coronary arteriography has been extensively studied and offers much of promise, but its application is subject to certain inherent limitations. Therefore, a second technique furnishing information about the structure of the coronary arteries might have value, particularly if it entailed no risk to the patient. It has long been known that calcifications in the coronary artery can occasionally be seen during cardiac fluoroscopy and many years ago it was predicted that these lesions could furnish useful diagnostic information if they could be visualized with regularity (Snellen and Nauta[24]). Recently a report has appeared which indicates that cinefluorography may offer an effective means to locate coronary calcification and so it seems possible that a new approach to patients with coronary disease may be at hand (Jorgins, Blank and Wilcox[11]). A review of the literature on coronary calcification and a pathologic study to determine the clinical significance of these lesions has, therefore, been performed.

Calcific lesions were among the earliest abnormalities to be recognized in the coronary arteries. The first known pathologic observations of coronary sclerosis were recorded in 1700 and within 3 years calcified lesions were described independently in Italy by Bellini (1643-1704) and in Germany by Thebesius (1686-1732). Other accounts of calcific coronary arteries in the 18th century were those of Morgagni (1682-1771), Senac (1693-1770),

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and Hunter (1728-1793). In addition to describing calcified coronary arteries, Hunter suffered angina pectoris and is known to have had coronary arteries that were found at necropsy to be "considerable ossified." In the 19th century, Cruveilheir (1791-1874) described "gangrene" of the myocardium following "calcareous infiltration" of the mouth of the coronary arteries[18]. In addition, Stokes (1804-1878)[26] reported a patient, aged 68, who died six weeks after being "suddenly attacked by symptoms resembling angina pectoris." The coronary arteries were "so completely converted into bone as to be quite solid, having no perceptible cavity, except at the distance of an inch from their origin." These early reports were based on gross inspection of the coronary arteries and calcification was considered to be the prime factor causing disease, possibly because calcific lesions tend to overshadow others. "During the 18th and 19th century, calcification was considered to be the very essence of coronary sclerosis" (Morgan[18]).

Current opinion accords calcification only an ancillary role in the genesis of coronary sclerosis. Blumenthal, Lansing, and Wheeler[2] suggest that it may be important in the initiation of atheromas but it is more common to consider calcification as an end stage of atheroma formation. Lansing, Blumenthal, and Gray[12] report that microscopic calcification appears in the internal elastic membrane of the coronary artery between 20 and 39 years of age and is associated with degeneration of elastic fibers and with early atheromas. Leary[13] considers atheromatous calcification a "terminal process, a monumental deposit in dead and dying tissue," and this view is widely accepted. Two sorts of microscopic techniques can be used to study calcific lesions, specific stains which require the continued presence of calcium and nonspecific stains which do not. Only early atheromas can be reliably studied by specific stains because heavily calcified lesions must be demineralized before microscopic sections can be cut. Hematoxylin and eosin stain is a nonspecific method which is applicable to study of advanced atheromas. It produces heavy, blue-black deposition of hematoxylin in the neighborhood of calcification, but does not locate the mineral deposit precisely (Cameron[5]). Hematoxylin is attracted to a ground substance where its binding does not require calcium but is influenced by the presence of trace amounts of iron and aluminum. Although microscopic techniques which can be applied to calcific atheromas do not precisely locate the deposition of mineral, they clearly indicate the nature of the underlying pathologic process. This has importance in considering the significance of calcific arterial lesions found by radiography because certain forms of medial calcification, notably Mönckeberg's medial sclerosis, rarely lead to vascular obstruction whereas advanced calcific atheromas frequently do. It is not always easy to distinguish Mönckeberg's medial calcification from atherosclerotic calcification by radiography, particularly when the two forms coexist, but this can be done by microscopy.

Microscopy of coronary arterial calcifications indicates that these lesions are invariably atherosclerotic. No explanation is available for the absence of Mönckeberg's medial calcification in the coronary artery, although the observation is an old one. The finding first appeared in a monograph on arterial disease published in 1912 by Faber[6]. Later, Mönckeberg confirmed Faber's observation[15]. Subsequent authors have not considered the matter in detail, but strong supporting evidence is found when the literature is

searched for case reports describing Mönckeberg's medial calcification of the coronary artery. Mönckeberg first described benign medial sclerosis in 1903[16] and careful search of the English and German literature from 1903 to 1958 has not disclosed a single convincing case of Mönckeberg's medial sclerosis in the coronary artery. The absence of benign medial calcification in the coronary artery does much to simplify the interpretation of coronary calcification discovered by radiography.

Because the observations of Mönckeberg and Faber were made almost half a century ago in Germany, it seemed wise to be certain that these findings remain valid in Americans today. Tejada, Gore, Strong, and McGill[28] have presented evidence that more calcium is deposited in the arteries of modern Americans than in others and it is possible that this increase might change the distribution of Mönckeberg's medial calcification. Therefore, a radiographic and histopathologic study of the hearts of residents of Los Angeles was performed. Eighty-nine hearts selected at random were radiographed after removal at necropsy. Next the coronary arteries were dissected off intact, and reradiographed. After this, coronary arteries were decalcified with EDTA, cut into 3 mm. segments, and examined microscopically. Thirty-five hundred arterial segments were examined and all calcific lesions visible by radiography were inspected. Atherosclerotic lesions were identified on the basis of their description in two recent publications (Moon[17], Saphir[21]); Mönckeberg's medial calcification on the basis of its description by Mönckeberg[16]. All radiopaque lesions were classified and all were atherosclerotic; the finding of Faber and Mönckeberg seems valid in present day Americans.

Two rare forms of nonatherosclerotic calcification require brief mention. One is a condition of infancy which is rapidly fatal and produces both vascular and myocardial calcification. This disease, which is of unknown etiology, appears to be a separate entity rather than a premature manifestation of adult coronary artery disease. According to Stryker[27], infantile coronary calcifications resemble lesions produced with toxic doses of vitamin D, more closely than they do atherosclerosis or Mönckeberg's medial sclerosis. In addition to infantile coronary calcification, a second nonatherosclerotic form of coronary calcification has also been reported to occur in patients with generalized calcinosis. Except for these two rare conditions, it seems safe to conclude that calcification of the coronary artery is pathognomonic of atherosclerosis.

Determination of calcium content by chemical assay indicates that the adult aorta may contain as much as 2 gm. of calcium per 100 gm. wet weight (Buck[4]). A preliminary survey by Bolick and Blankenhorn[3] indicates that normal coronary arteries contain approximately 50 mg. calcium per 100 gm. wet weight and that advanced coronary atheromas may contain as much as 1.4 gm. calcium per 100 gm. wet weight. There is evidence that diffuse deposition of calcium can occur in arteries with increasing age (Buck[4], Haythorn *et al.*[9], Hevelke[10]) and Haythorn, Taylor, Crago, and Burrier[9] suggest that two independent processes affect arterial walls; diffuse calcification of elastic fibers as they age, discrete calcification of atheromata as they become more severe. In the coronary artery all visible calcific lesions are discrete and are associated with atheromas. If diffuse calcification occurs, this is not visible by radiography.

The first radiographs of calcific coronary arteries were published in 1903

by Simmonds[23] who studied hearts excised at necropsy and stated that the radiographic pattern of calcification exhibited a characteristic appearance, calcium-free areas alternating with calcium laden ones along major coronary branches. Pyke and Symons[20] radiographed the hearts of 72 consecutive persons coming to necropsy in London and found that 53% had calcific lesions in the coronary artery. Blankenhorn and Stern[1] radiographed 76 unselected patients, necropsied in Los Angeles, and found an incidence of 43%. Coronary calcification can be found more frequently by postmortem radiography than by gross or microscopic examination because a more comprehensive search is possible. Coronary calcifications were more common than any other calcific lesions in the heart in both the series of Blankenhorn and Stern and that of Pyke and Symons. Sosman[25] also found that coronary calcifications outnumbered any other calcific cardiac lesion and this was true in an unpublished study by Felson[7]. Examination of the heart by radiography at postmortem examination emphasizes the prominence of calcification in the pathologic picture of coronary sclerosis. It makes more understandable the view of early workers who were guided by gross appearance and considered calcification "the very essence of coronary sclerosis" (Morgan[18]).

When radiopaque media are used to fill the coronary arteries for postmortem radiographs, the result is entirely different because calcific densities are obscured. Calcific lesions are not mentioned in numerous studies carried out in this manner. Schlesinger found that calcific lesions in an occluded segment of artery can be mistaken for the injection mass and give the erroneous appearance of a patent vessel[22]. Few investigators have radiographed the heart before and after injecting the coronary arteries because satisfactory filling appears to require that injections be made immediately after the heart is removed. However, van der Straeten performed postmortem radiographs before and after injecting Lipiodol in 34 hearts from aged individuals with known heart disease[29]. Calcific lesions were found in 31 of the 34. All vessels which showed stenotic areas in the coronary artery also showed calcific lesions but the degree of stenosis could not be predicted from the extent of calcification. Coronary arteries free of calcification showed no stenotic areas. Sixteen of the hearts examined by van der Straeten exhibited myocardial infarction and of these, 14 had calcification in the coronary arteries. Thirteen of 14 hearts with myocardial infarction radiographed by Blankenhorn showed calcific lesions.

Calcific densities in the coronary artery occur in three major radiographic patterns (Blankenhorn and Stern[1]). The most common calcific lesions are small, discrete, punctate areas varying from 1 to 10 mm. in greatest diameter. Dense, blocky shadows which completely outline the coronary wall for a distance of 6 to 30 mm. are the next most common pattern. Least common is a series of punctate lesions scattered for a considerable distance along the artery in a manner giving the general appearance of a railroad track viewed from above. One heart has been encountered with 450 mm. of the coronary arterial system outlined by track-like calcifications. Microscopic examination indicates that advanced atheromas are responsible for all calcific patterns, although lesions which produce the track-like pattern are often flatter and more widely scattered than those which underlie blocky or punctate lesions. This characteristic may be responsible for the length attained by

track-like calcification because it allows them to be tolerated sufficiently long to grow. It also seems possible that the heavy accumulation of calcium in one area of atheromatous change seen with dense, blocky calcific patterns may not be tolerated for a sufficient period to grow longer than 35 mm.

A small amount of evidence suggests that calcific lesions in young individuals may have ominous portent out of all proportion to their size. The author has been able to radiograph the hearts of 8 individuals between 30 and 50 years of age who died suddenly of ischemic heart disease. Five of the 8 showed calcific lesions in the coronary artery. The youngest patient, a man of 32, exhibited two radiopaque areas 1 mm. in diameter which were the site of advanced occlusive coronary disease (Fig. 1). It appears unlikely that lesions only 1 mm. in diameter can be visualized in living man with any present technique, however, the lesions shown in Fig. 2 might well have been seen with cinefluorography. Figure 2 illustrates the coronary arteries of a 45-year-old mechanic who collapsed while working under an automobile and died shortly thereafter.

Fig. 1.—Microscopic detail of a radiopaque lesion found in the anterior descending branch of the left coronary artery of a man, aged 32, who died suddenly of ischemic heart disease. H & E stain times 30. Parts of the heavily calcified portion of the lesion were torn during sectioning.

In certain aged individuals extensive calcific coronary atheromas may not cause ischemic heart disease. Frequently, these hearts show track-like calcifi-

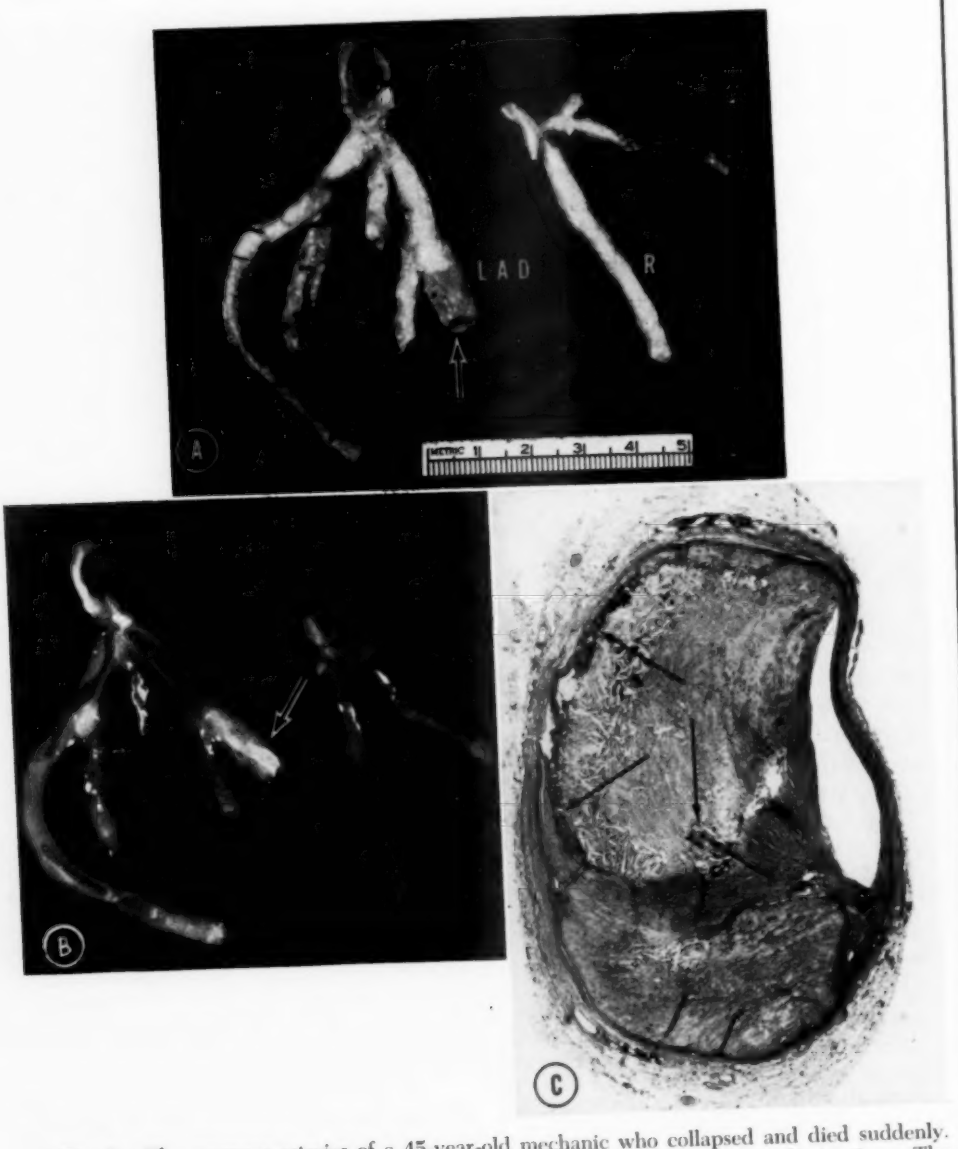

Fig. 2.—The coronary arteries of a 45-year-old mechanic who collapsed and died suddenly. *A.* The arteries dissected from the heart. The right coronary artery is diminutive. The arrow indicates the site of an occlusive lesion in the anterior descending branch of the left coronary artery.

B. A contact radiogram of these arteries showing calcific lesions.

C. Detail of the radiopaque area indicated by the arrow in "*B*." H & E stain times 25. Areas of heavy hematoxylin staining are indicated.

cation and although advanced atherosclerosis is present, other factors appear to ameliorate its effect upon the myocardium. The coronary arteries are often quite large, at times almost aneurysmal, and it may be the size of these arteries which allows extensive atherosclerosis without myocardial ischemia. Lesions of this sort should be easily visible by radiography in living man. In fact, there is reason to believe that the majority of calcific coronary lesions visualized prior to the use of cinefluorography were of this sort.

Radiographic study of coronary calcification in living man began in 1927 with a report from Vienna by Lenk[14]. During fluoroscopy a 68-year-old man, without cardiac symptoms, was found to have a left ventricular aneurysm. Roentgenograms employing a Bucky diaphragm were made and these showed, in addition to the aneurysm, two parallel calcific densities which Lenk felt to be in the wall of the left coronary artery. In 1933, Parade and Kuhlmann[19] reported 3 additional cases with calcified left coronary arteries. These original reports met with considerable skepticism because it was felt that pericardial calcification had been seen. However, in 1934, Wosika and Sosman[30] reported a case in which extensive calcification of both coronary arteries visualized during life was proven at necropsy and following this the original reports received acceptance.

In 1937, Snellen and Nauta[24] reported 40 cases found within a one-year period, 5 of these had the diagnosis confirmed by necropsy later. In addition to employing fluoroscopy, Snellen and Nauta searched for coronary calcification with short exposure roentgenograms employing a Bucky diaphragm. The proper positioning of patients during fluoroscopy was also studied by Snellen and Nauta who demonstrated that: antero-posterior views of the heart favor visualization of the left anterior descending branch of the left coronary artery, right oblique views favor visualization of the right coronary artery, and left oblique views favor visualization of the circumflex coronary artery. Snellen and Nauta were of the opinion that with improved techniques, roentgenography might prove useful for clinical diagnosis of coronary artery disease.

Habbe and Wright[8] reported a routine search for coronary calcification in all patients over 40 years of age. Fluoroscopy was used and short exposure spot films made over the precordium. With this combination, Habbe and Wright demonstrated that approximately 3% of their patients showed coronary calcification. One-third of the patients exhibiting calcification were between 50 and 60 years of age; the remainder over 60 years of age. According to Habbe and Wright, the significance of calcified coronary arteries must be decided on an individual basis after clinical evaluation of the patient. In general, the younger the patient, the more important the finding.

Prior to the advent of cinefluorography, all radiographic studies in living man uncovered an incidence of calcification only a fraction of that found at necropsy but the calcifications reported were much larger. The greatest incidence of calcification discovered during life was 3%, the smallest incidence reported at necropsy was 40%. The usual calcifications found in living man (as judged from available illustrations) were longer than 35 mm.; only one in 10 calcifications found at necropsy exceed 35 mm. Pathologic evidence suggests that large calcifications are not the most important in production of ischemic heart disease and it seems

likely that lesions of great clinical significance have been overlooked.

Cinefluorography is now being used by a number of workers to search for coronary calcification and one comprehensive report has appeared which describes its use. Jorgins, Blank, and Wilcox[11] report on 803 cinefluorographic examinations performed in a Veterans hospital. Two hundred twenty-five patients showed calcification of the left coronary artery, 58 patients showed calcification of the right coronary, and 38 patients showed combined lesions of both coronary arteries. Lesions as small as 2 mm. were seen. These findings suggest that cinefluorography may discover an incidence of calcific coronary lesions in living man approaching that which can be found by radiography at necropsy. If continued experience bears out this report, cinefluorography should offer much in diagnosis and evaluation of patients with coronary sclerosis. It would appear likely to be useful as a case finding method and should serve to augment other diagnostic measures. In addition, it might prove of value in population surveys as a direct means to determine the incidence of atherosclerosis for correlation with studies of diet or other factors. An extensive trial of this technique seems indicated because visualization of calcific lesions of the coronary artery offers one safe means to furnish definitive evidence as to the nature and distribution of coronary atherosclerosis in living man. However, it should be borne in mind that the most significant coronary calcific lesions to be searched for may not be the longest or those most easily seen.

Summary. Calcific lesions of the coronary artery do not presently receive as much attention as was accorded them in former years. In adult Americans, visible calcific coronary lesions are invariably atherosclerotic. Review of the English and German literature from 1903 to 1958 reveals no convincing case of Mönckeberg's medial calcification of the coronary artery. Examination of 3500 segments of adult coronary artery by a combination of postmortem radiography and microscopy demonstrates that all visible calcific lesions are atherosclerotic. A rare condition of infancy which is fatal may cause nonatherosclerotic coronary calcification.

Postmortem radiography without injection of radiopaque material (which obscures calcified lesions) indicates that the most common calcific lesion in the heart of Americans is a coronary calcification. The extent of coronary calcification is not always paralleled by the severity of ischemic heart disease which results, because dilated coronary arteries may become extensively calcified without becoming occluded and occlusive lesions may be lethal before they are extensively calcified. On the other hand, approximately 90% of hearts with myocardial infarction exhibit one or more calcific coronary lesions. In addition, 5 of 8 hearts from patients dying suddenly of ischemic heart disease between the ages of 30 and 50 showed calcific lesions visible by postmortem radiography.

Fluoroscopy, with the conventional techniques presently used, reveals only a small fraction of coronary calcifications which are present in living man. Cinefluorography offers promise as an effective means to identify coronary calcification and deserves extensive trial as a case finding technique.

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SUMMARIO IN INTERLINGUA

Calcification del Arteria Coronari: Un Revista

Lesiones calcific del arteria coronari non recipe currentemente le grado de attention prestate a illos in annos passate. In adultos american, visibile lesiones calcific del arteria coronari es invariabilemente atherosclerotic. Un revista del litteratura de lingua anglese e de lingua german ab 1903 ad 1958 ha revelate nulle convincente caso del calcification medial del arteria coronari del typo de Mönckeberg. Le examine de 3500 segmentos de adulte arteria coronari per un combination de radiographia e microscopia post morte ha demonstrate que omne le visibile lesiones calcific esseva atherosclerotic. Un rar condition de infantia, que es mortal, pote causar non-atherosclerotic calcification coronari.

Radiographia post morte sin injection de substantia radio-opac (que tende a obscurar le calcificate lesiones) indica que le lesion calcific le plus commun in le corde de americanos es un calcification coronari. Le grado del calcification coronari non es in omne casos in parallela con le severitate del resultante ischemia cardiac, proque dilatate arterias coronari pote devenir extensemente calcificate

sin devenir occludite e occlusive lesiones pote devenir letal ante que illos es extensemente calcificate. Del altere latere, approximativemente 90% del cordes con infarcimento myocardial exhibi un o plure calcific lesiones coronari. In plus, 5 inter omne 8 cordes de patientes subitemente morte con ischemic morbo cardiac a etates de inter 30 e 50 annos monstrava lesiones calcific visibile in radiographia post morte.

Fluoroscopia, con le uso del technicas que es currentemente de routine, revela solmente un micre fraction de calcificationes coronari presente in patientes in vivo. Cinefluoroscopia es promittente como medio efficace pro le identification de calcification coronari e merita extense essayos como technica pro le detection de casos.

SUMMARIO IN INTERLINGUA

(See page 11 for original article)

Le Uso Prolongate, le Effectos Lateral, e le Toxicitate de Acido Ethylenediamina-Tetraacetic Dinatric (AEDT)

In le curso de un periodo de duo annos, duo milles consecutive infusiones de acido ethylenediamina-tetraacetic dinatric (AEDT) esseva administrate a 81 subjectos in un studio del efficacia de iste agente in le therapia de morbo de arteria coronari. Nos ha incontrate nulle serie effectos lateral e nulle serie toxicitate in le uso de AEDT dinatric quando illo esseva administrate in doses de 3 g infundite como solution de 0,5% in le curso de 2½ a 3 horas. Nos opina, per consequente, que le droga pote esser usate sin periculo durante prolongate periodos de tempore.

Le plus serie effecto lateral que on ha attribuite a iste agente es su nephrotoxicitate, sed con le hic-describite methodos de administration nulle tal injurias se faceva manifeste. Viste que il pare que toxicitate renal pote occurrer con dosages de 5 g o plus, le adoption del dosage plus basse es recommendate. (Le Consilio pro Drogas in le Association Medical American recommenda un dosage de 5 g.)

Quanto al altere effectos notate, nos mentiona hypotension, hypocalciemia, arditura in le sito del injection, thrombophlebitis, e symptomas gastrointestinal que omnes esseva infrequente. Nulle signo esseva vidite de reactiones systemic, de reactiones histaminoide, de anemia, de dermatitis, e de hyperglycemia (o glycosuria) como illos se trova describite in previe reportos in le litteratura. AEDT pote esser administrate sin risco de discalcification ossee.

Con respecto al programma de administration, nos nota le facto que nostre plano de infusiones omne secunde die esseva therapeuticamente efficace e que nos ha le impression que illo comporta minus effectos lateral que le usualmente reportate methodo de septe consecutive dies de therapia omne secunde septimana. Le decision de laborar con 20 infusiones in omne curso therapeutic esseva arbitrari. Currentemente nos studia le maximo de efficacia (excretion de calcium) con varie periodos de tractamento.

THE LONG TERM USE, SIDE EFFECTS, AND TOXICITY OF DISODIUM ETHYLENEDIAMINE TETRAACETIC ACID (EDTA)*

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Chelation, as a therapy for lead poisoning, is well known and descriptions relative to the clinical use of chelating agents are generally confined to this particular condition. The recently proposed uses of metal binding methods in a variety of other diseases (requiring long term administration of chelating agents) have produced problems of dosage and administration unlike those encountered with lead poisoning and have created a need for current definition of the toxicity of the chelating agents.

That undesirable metals, other than lead, could similarly be bound within the ring structure of the chelating agent and thus removed from the body prompted attempts to chelate calcium, iron, copper, among other metals. The success of these trials had obvious implications and chelation therapy has been investigated in a variety of diseases associated with excessive amounts of certain metallic ions. There have been recent reports to indicate a potential usefulness of chelation in Wilson's disease (Bickel, Neale and Hall[2], Scheinberg and Sternlieb[29], Zimdahl, Hyman and Stafford[37]), scleroderma (Klein and Harris[15], Mendelson[20], Rukavina *et al.*[27]), heavy metal intoxications (Kneller, Uhl and Brem[16], Fenalver[21], Rieders[25], Rieders, Dunnington and Breiger[26], Spencer, Samachson and Laszlo[33]), sarcoidosis (Rukavina, Orkin and Lynch[28]), iron storage diseases (Figueroa *et al.*[8], Greenwalt and Ayers[11], McMahon[17]), porphyria (Peters *et al.*[24]), metastatic calcinosis (Clarke, Clarke and Mosher[3]), myositis ossificans (Unpublished data[35]), coronary artery disease (Clarke, Clarke and Mosher[3], Kitchell, Meltzer and Seven[14], Meltzer, Ural and Kitchell[19]), calcareous valvular disease (Kitchell, Meltzer and Seven[14]), cerebral and peripheral arteriosclerosis (Kitchell, Meltzer and Seven[14], Meltzer, Palmon, and Kitchell[18]), as well as the treatment of digitalis toxicity and other cardiac arrhythmias (by induced hypocalcemia [Gubner and Kallman[13], Soffer *et al.*[32], Surawicz *et al.*[34]]).

This report concerns our experience with the long term use of the chelating agent disodium ethylenediamine tetraacetic acid (EDTA) in terms of method of administration, side effects, and toxicity.

Method of Study. During a 2-year period we observed 81 patients who received a total of 2000 consecutive infusions of disodium EDTA as part of a preliminary investigation of the effectiveness of this agent in the treatment of coronary artery disease.

The distribution of patients and the num-

*This work was supported by a grant from the John A. Hartford Foundation.

ber of infusions received is shown in Table 1. The 19 patients who received less than 10 infusions were either normal subjects or persons with cardiac arrhythmias who were observed and treated for less than 3 months. The remaining 62 subjects have now been followed from 8 to 30 months.

TABLE 1.—DISTRIBUTION OF PATIENTS ACCORDING TO TOTAL NUMBER OF INFUSIONS

Number of Patients	*Total Number of Infusions*
19	1–10
30	11–20
19	21–40
9	41–60
1	61–80
3	81–120

All of the patients received the chelating agent in the same manner and under the same circumstances. Since we believe these conditions to be a significant part of our data and since we have found this particular method of administration to be successful, the program is described in detail.

The subjects were all outpatients in a research clinic designed for this study. While resting in lounge type chairs, they received intravenous infusions containing 3.0 gm. disodium EDTA (Endrate) in 500 ml. normal saline or glucose solution. (The choice of 3.0 gm. dosage is explained in later paragraphs.) During the course of the infusion they were under constant nursing care and never unattended. Blood pressures and pulse rates were recorded at 30-minute intervals and questionnaires relative to side effects were completed at the end of each infusion and prior to the succeeding treatment. One of us (F.P.) saw each patient who described any symptoms during or after infusion.

The infusions were given through disposable equipment and lasted from 2½ to 3 hours. If the patient experienced burning at the site of venipuncture or if any other symptom developed the nurses slowed the rate of infusion and recorded the difficulty. The treatments generally were given on alternate days (3 times weekly) although several patients received 2 or 4 infusions a week varying with their personal schedules. The program was continued in this manner until a total of 20 was reached (usually 6 to 8 weeks). At this time all therapy was discontinued (a rest period) for 6 to 8 weeks. The rest period has been found important, for reasons not yet known, since it was not until then that the desired clinical effect occurred (in this study, improvement in the anginal syndrome). After the rest period a second series of 20 infusions was started in the same manner and additional series followed if indicated clinically. One patient has received 6 full courses thus far.

A series of studies were performed on each patient prior to therapy and at monthly intervals thereafter. These included detailed investigations of the cardiovascular system and of calcium metabolism (which were our basic problems in this project) as well as complete blood count, urinalysis, blood urea nitrogen, blood sugar, serum protein (and A/G ratio), prothrombin time and cholesterol. At least 10 different patients had each of the following studies: thyroid function (protein bound iodine and I_{131} uptake); liver function tests (Bromsulfalein, flocculations, turbidity); PSP dye excretion; serial Roentgen-ray examination of the hands (with graded density scales to discern any possible decalcification) and blood coagulation screening studies.

During the period of this study 4 necropsies were performed on patients who had received 60, 33, 22, and 8 infusions of EDTA respectively prior to death.

Results. The reported side effects and toxicity of EDTA have been collected by Seven[30]. Table 2 summarizes the incidence of these effects he described as noted in our series of 2,000 consecutive infusions containing 3.0 gm. disodium EDTA.

A. RENAL DAMAGE. The most potentially dangerous effect of EDTA has been considered nephrotoxicity. Dudley *et al.*[7], in 1955, reported 2 deaths occurring in patients being treated with disodium EDTA (for hypercalcemia) with dosages exceeding 5 gm. daily where renal tubular epithelial degeneration occurred. Foreman, Finnegan and Lushbaugh[9] described transient, but significant, urinary findings (albuminuria, cylindruria, hematuria, renal cells) in a laboratory worker who was contaminated with plutonium and was treated with daily infusions of 5 gm calcium disodium EDTA. Subsequently, this same group evaluated the

nephrotoxic potential of EDTA in rats and demonstrated a relationship between dosage and renal tubular destruction (Foreman, Vier and Magee[10]). They concluded from these data that a dosage of 50 mg. per kg. per day would be safe for humans (3.5 gm. in a 70-kg. man). Other reports in the literature would seem to verify their work. Vogt and Cottier[36] describe the necropsy findings of a 38-year-old man being treated for lead poisoning, who, by error, received 600 mg. calcium EDTA per kg. per day for 4 days which

TABLE 2.—SIDE EFFECTS OF EDTA ADMINISTERED WITH 2000 INFUSIONS

Side Effect	*Frequency of Occurrence*
A. RENAL DAMAGE (increase in BUN, decrease in PSP excretion, cylindruria, hematuria, or persistent albuminuria greater than 1+	0
B. BURNING AT INJECTION SITE or along course of vein:	
Initially only,	30
Throughout infusion,	68
C. THROMBOPHLEBITIS	1
D. HYPOTENSION: Mild: a drop of systolic pressure of 20 mm. without symptoms	8
Moderate: a drop of systolic pressure of 30 mm. with or without symptoms	23
Severe: a drop of 30 mm. or more with distinct hypotensive symptoms	2
E. HYPOCALCEMIA: Mild: numbness, tinkling at circumoral area or leg cramps or muscle spasm	20
Severe: signs of tetany (Chvostek's sign, and others) or fall in serum calcium to 7 mg./100 ml.	0
F. SYSTEMIC REACTIONS (febrile reaction, malaise, fatigue, headache, anorexia)	0
G. HISTAMINE-LIKE REACTION (sneezing, lacrimation, nasal congestion)	0
H. ANEMIA or other hematopoietic changes related to treatment	0
I. GLYCOSURIA OR HYPERGLYCEMIA	0
J. DERMATITIS (presumably due to pyridoxine deficiency)	0
K. NAUSEA + VOMITING: Mild	15
Moderate	1
Severe	2
ABDOMINAL CRAMPS OR PAIN	2

resulted in a necrotizing nephrosis. Reports of nephrotoxicity have occurred most often in patients receiving EDTA as a therapy for lead poisoning, causing some suspicion that the heavy metal poisoning *per se* could contribute to the renal findings.

From our observations a dosage of 3.0 gm. disodium EDTA would appear to be without danger of nephrotoxicity. We found no evidence of elevation of urea nitrogen, decreased PSP excretion, cylindruria, hematuria, renal cells, or persistent significant (greater than 1+) albuminuria in any patient during this period. The 4 necropsies showed no evidence of nephrosis or other renal damage despite prolonged administration of EDTA.

B. BURNING AT INJECTION SITE OR ALONG COURSE OF VEIN. Burning at site of venipuncture was the commonest complaint we encountered. This occurred 98 times (30 at the start, 68 throughout the infusion) or 4.9%. This is a much lower incidence than one would expect from the literature and is undoubtedly the result of careful, specialized nursing care.

C. THROMBOPHLEBITIS. Thrombophlebitis occurred once in one patient after 18 infusions. This was localized and cleared promptly after 7 days of rest from treatment. On many patients it has been necessary to use the same vein for repeated infusions without producing phlebitis.

D. HYPOTENSION. Orthostatic hypotension may occur during an infusion. The chair type position we employ probably minimizes this problem, which occurred 33 times. If the patient is treated in bed, care should be taken to prevent this postural hypotension at the completion of the infusion. On 2 occasions patients with moderate hypertension experienced distinct hypotensive symptoms during the course of an infusion with associated lowering of the blood pressure 40 to 50 mm. These findings and symptoms were short lived. The mechanism of hypotension is not clear but may represent the chelation of a pressor substance. (It has been reported that the antihypertensive agent, hydralazine, exerts its effect by chelation [Comens[5]].)

E. HYPOCALCEMIA. Hypocalcemia can occur if the chelating agent is administered too rapidly, as would be anticipated. By controlling the rate of infusion so that 3.0 gm. EDTA was given during a 2½-3 hour period, mild symptoms of hypocalcemia occurred only 20 times in 2,000 infusions. The initial symptom is most often numbness and tingling circumorally. By slowing the rate of administration the symptoms generally disappear. Frank tetany never occurred in any patient.

F. SYSTEMIC REACTIONS. We observed no evidence of a systemic reaction to EDTA as described by Seven[31]. The syndrome presumably involves chills, fever, back pain, muscle cramps, vomiting and frequency of urination, all occurring 4 to 8 hours after an infusion and subsiding within 12 hours. If such a reaction is related to EDTA its infrequency is evident from this study. The only systemic manifestation perhaps attributable to this therapy was a period of asthenia and lethargy described by several patients for 24 hours following an infusion. This did not occur with regularity nor were we able to see any relationship to any particular factor, so that a specific conclusion could not be reached regarding the etiology.

G. HISTAMINE-LIKE REACTION. We did not see a histamine-like reaction (with sneezing and lacrimation) to EDTA in any subject, and it would appear unlikely that this effect could be a problem, from our experience.

H. ANEMIA OR OTHER HEMATOPOIETIC CHANGES. No hematopoetic changes re-

lated to therapy were observed during this 2-year period. It has been suggested that anemia may occur after prolonged therapy (by chelating iron or other hematopoietic metals) but this has not been the case and no such effect was demonstrated.

I. GLYCOSURIA OR HYPERGLYCEMIA. Chelation had no effect on blood sugar levels and glycosuria never occurred as a result of therapy in nondiabetic subjects. In patients with known diabetes, who were receiving insulin, a hypoglycemic effect was demonstrated on several occasions demanding a reduction in insulin requirement. The mechanism of this effect is to be considered in a separate publication.

J. DERMATITIS. An interesting dermatitis has been described on several occasions seemingly related to chelation therapy (Clarke, Clarke and Mosher[4], Perry and Schroeder[22,23]). This is a crusting lesion involving the lips and nose and attributed to a drug-induced pyridoxine deficiency. We commented, in a previous publication[19], on the absence of this finding among our earlier patients, and during this further investigation we still have not seen this dermatitis. It is difficult to reconcile the discrepancy between other reports and our experience.

K. NAUSEA AND VOMITING. Gastrointestinal symptoms were infrequently noted in this study with nausea and vomiting occurring on 18 occasions and abdominal, cramping pains twice. None of these reactions were serious and their etiology is unknown.

OTHER EFFECTS OF EDTA. 1. *Embolization.* Clarke, Clarke and Mosher[3] suggested the danger of embolization after EDTA therapy for calcareous cardiovascular disease, implying that decalcification could occur unevenly, allowing a weakened piece of calcium to free itself from a larger mass. He described 2 cases of suspected calcium embolism and one case in which he thought this had occurred. We have not had any suggestion of this serious possibility but it is not inconceivable that this threat could exist.

2. *Decalcification of Bone.* There is the unfounded fear that chelation over a prolonged period of time will produce decalcification of bone. Considering that each gm. EDTA chelates about 110 mg. (300 to 350 mg. per 3.0 gm. infusion) and that the body's calcium reserve is 20 gm. (Copp[6]), it would be unlikely that this reserve could ever be depleted so that the chelating agent would affect bone. (The basic concept of the use of disodium EDTA in calcific diseases is that the chelating agent removes calcium from the serum which is promptly replaced from the calcium reserve which in turn is restored by loosely bound calcium from metastatic [blood vessels, and others] sites, thus producing a beneficial effect.)

We have studied the bones of the hands and wrists of 14 patients with serial roentgenographic examinations using graded densities for comparative purposes and have seen no change in density to suggest decalcification.

3. *Concurrent Use with Other Medications.* The use of chelating agents and other medications (antihypertensive, and others) concurrently was of concern originally. Subsequent observations have not indicated any variation of drug action because of chelation and there is no need to discontinue previous therapies during the course of this treatment. Although we have discussed the effect of EDTA on the cardiovascular system elsewhere[14], the use of this agent with digitalis is of interest here. It is known that drug induced hypocalcemia will allow potassium to re-enter the myocardial cell and antagonize the digitalis effect. This knowledge has been put to clinical advan-

tage wherein EDTA can promptly reverse digitalis toxicity and other arrhythmias. In patients receiving digitalis (not toxic) who are given EDTA the effectiveness of digitalis is lost during the period of infusions but returns promptly thereafter and is consequently no problem.

4. *Thyroid Function.* The effect of EDTA on thyroid function was of considerable interest as some question arose theoretically over the possibility of chelation depressing this function and relieving angina (Gubner[12]). Our studies with protein bound iodine levels and I_{131} uptakes before and after courses of EDTA in 10 patients showed no goitrogenic effect.

5. *Prothrombin Time.* The prothrombin time falls about 30% during the course of each infusion but returns to pretreatment levels usually within 12 hours. This is secondary to calcium bondage and excretion. We have investigated other coagulation effects related to this agent but our data are still incomplete.

Summary. Two thousand consecutive infusions of disodium EDTA were given to 81 subjects in a study of the effectiveness of this therapy in coronary artery disease during a 2-year period. We have found no serious side effects or toxicity with the use of disodium EDTA when administered as a 3-gm. dose and infused as a 0.5% solution over 2½ to 3 hours. It is, therefore, our opinion that the drug can be used without danger over prolonged periods.

The most serious side effect ascribed to this agent has been nephrotoxicity, but with the administration methods described here there has been no evidence of such damage. Since it would appear that renal toxicity can occur with dosages of 5 gm. or more, it is recommended the the lower dosage be adopted. (The Council on Drugs of the American Medical Association advises a 5-gm. dosage[1].)

Relative to other effects, we observed hypotension, hypocalcemia, burning at site of injection, thrombophlebitis, and gastrointestinal symptoms infrequently and saw no evidence of systemic reactions, histamine-like reactions, anemia, dermatitis, hyperglycemia (or glycosuria) as described in previous literature. EDTA can be administered safely without danger of bone decalcification.

Concerning the program of administration, our plan of alternate day infusions has been therapeutically effective and we have the impression that there are less side effects than with the usually designated method of 7 days therapy, 7 days rest. The choice of 20 infusions as a course of treatment was arbitrary. We are currently studying the maximum effectiveness (calcium excretion) with varying periods.

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(Interlingua on page 10)

A CRITICAL ANALYSIS OF MORTALITY ASSOCIATED WITH DELIRIUM TREMENS

REVIEW OF 39 FATALITIES IN A 9-YEAR PERIOD*

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Since Thomas Sutton[28] first coined its present name in 1813, delirium tremens has been categorized as a potentially fatal disease. Although it is generally recognized that within the past 50 years the mortality rate associated with this disease has markedly declined, this particular phenomenon is difficult to assess. There appear to be multiple factors which contribute to the mortality rate, and because of the variable nature of these factors, as well as the unscientific evaluation of effective therapy, the relative value or ineptitude of our present methods of treatment remains obfuscated. In order to plan more rational therapy of this disease, attention first must be directed toward the multiple factors which account for death.

For over a century, since Armstrong[2] in 1813 first suggested withdrawal from alcohol as a possible cause of delirium tremens, a battle has raged concerning this point, and it was not until a monumental paper by Isbell and coworkers[19] was published in 1955 that we finally obtained some definite insight into the relationship of delirium tremens to abstinence from alcohol. This group demonstrated clearly, using volunteers, that delirium tremens could be produced only by rapidly falling blood alcohol levels, which, in most instances, was tantamount to alcohol withdrawal. They also gave convincing evidence that delirium tremens is a syndrome similar to that which follows abstinence from barbiturates (and probably paraldehyde) in subjects chronically addicted to these agents. The severity of symptoms appeared to vary roughly with the duration of addiction, a 48-day period of continuous alcohol intoxication being necessary to bring about a full blown delirious state on withdrawal.

Our purpose in this paper is to analyze a series of fatalities associated with delirium tremens in the current era and to point out prognostic signs and possible means of preventing many such deaths in the future.

Material and Method. This study includes all cases of delirium tremens observed at the Philadelphia General Hospital from January 1, 1950, to December 31, 1958. The case records of all fatalities in which delirium tremens was listed as a primary or associated diagnosis were reviewed. It was decided to include only those cases manifesting increased motor activity in the form of tremors or convulsions in association with disorientation and hallucinations or frank delirium; cases lacking any of the above criteria were excluded. A total of 39 eligible cases was found

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and critically analyzed for history, physical findings, laboratory and roentgenographic data, hospital course, therapy, and necropsy findings.

During the same period, 250 patients were admitted on 291 occasions and survived episodes of delirium tremens. These records were studied also for criteria for diagnosis, presence of complicating factors, presence of convulsions, temperature course, and therapy.

Results. FATAL CASES. Thirty-six of the 39 fatalities were inextricably associated with the delirious state; in the remaining 3 cases it appeared that the delirium tremens itself had largely subsided at the time of death and probably, therefore, contributed slightly, if at all, toward death. In 18 cases, death appeared to result almost solely from the delirium tremens in the absence of lethal complicating diseases.

TABLE 1—SUMMARY OF CLINICAL FINDINGS IN THE FATAL GROUP OF 39 CASES

Pulmonary symptoms and signs		21
Temperature of 104° or more		20
Probable liver enlargement		19
Vascular hypotension (terminal)		19
Traumatic lesions		13
Fractures	6	
Malnutrition		13
Dehydration		12
Convulsive seizures		12
Gastrointestinal symptoms and signs		11
Hypertension		9
Decreased deep tendon reflexes		5
Increased deep tendon reflexes		4
Ascites		4
Cardiomegaly		4
Gastrointestinal hemorrhage		3
Headache		3
Focal neurologic signs		3
Ileus		3
Cellulitis		2
Icterus		2

The duration of hospitalization varied from 2 hours to 23 days, but in the group dying while in delirium tremens, the maximum duration was 12 days, with a mean of 3.4 days. Eight cases were hospitalized for less than 24 hours. Twenty-five patients entered the hospital already in a state of delirium tremens; the remainder developed the full-blown clinical syndrome within 72 hours after admission.

CLINICAL FINDINGS. From Table 1, one can obtain an overall impression of the frequency of various manifestations in the ultimately fatal cases.

All of the patients were severe chronic alcoholics, many of whom had had one or more antecedent episodes of delirium tremens. A definite history of a recent alcoholic spree was obtained in 13 cases, lasting from one week to several months. Patients were admitted with diverse symptoms and signs. In addition to symptoms related to obvious physical trauma and to other complicating illness, many were related to gastrointestinal dysfunction, which included nausea, vomiting, diarrhea, and epigastric pain.

Accurate physical examination was difficult to accomplish on a number of individuals because of poor patient cooperation. However, it was possible to glean the following pertinent information: In all cases where specifically mentioned, poor hydration was present. Admission blood pressures showed a tendency toward elevation, about one-fourth were at 140/90 or higher. Pulse and respiration were generally elevated and commensurate with the degree of activity, fever, and complicating illness.

Congestive heart failure was clinically present in only one case; no satisfactory explanation was given for its presence and no necropsy was obtained.

Regarding the occurrence of gastrointestinal hemorrhage in 3 patients, it should be explained that 2 were severe and resulted from esophageal varices, and the third was mild and developed from an unknown site.

Of the 3 cases manifesting focal neurologic signs, in 2 instances these

changes appeared after convulsive seizures, and in a third, hemiparesis followed head trauma. (Necropsies performed in the first 2 revealed no striking abnormalities in the brain; in the third, no postmortem examination was done.)

Convulsive seizures were quite common within the fatal group. One individual had a unilateral clonic seizure (brain negative at necropsy, mentioned above). Another patient suffered a Jacksonian seizure (brain not examined). The remaining patients manifested generalized grand mal episodes. Nine of the 12 having convulsions also developed peak temperatures of 104° or greater. The convulsions occurred at sundry times during the course of the illness: usually at the onset of the delirious state, but occasionally as a preterminal phenomenon. In 6 cases, more than one convulsion was observed.

During the patients' stay in the hospital, hyperthermia became quite prevalent. The highest recorded temperature was 108° (rectally). A fairly close correlation was found between hyperthermia and convulsions. In 11 cases, hyperthermia seemed to result from the delirious state *per se* in the absence of other causative factors. The onset of withdrawal symptoms could be accurately dated in 8 of these latter cases, and in all, death occurred 3 to 4 days following the onset of symptoms, coinciding with the time of maximum temperature elevation.

It was noted that at the time of admission an odor of spirits could be detected on the breath of 6 patients. Three of these patients were admitted with hip fractures, the fourth was brought in shortly after a grand mal seizure, and the fifth was admitted complaining of abdominal pains. The remaining patient entered the hospital with far-advanced cirrhosis. It is important to note that, in all of these cases, delirium tremens was not manifest upon admission. Rather, initial hospitalization usually was prompted by severe and urgent symptoms which in all probability stemmed from and abruptly terminated the alcoholic spree. Once these patients were within hospital walls and were denied further access to alcohol, withdrawal symptoms developed quickly, usually within 8 to 24 hours after admission. The full-blown delirious state supervened within the next 48 hours. Five of these patients developed hyperthermia which became apparent on the second to fourth hospital day, reaching the maximum value on the day of death.

From Table 3 one can see that major complicating factors were exceedingly common, with liver disease and pneumonia being most prevalent. Pulmonary tuberculosis was considered to be active in 3 cases.

The illness frequently was terminated by a short period of coma, and in many cases, vascular hypotension occurred, frequently in association with a rapid pulse and respiration. Nineteen patients clearly manifested such derangements in vital signs prior to death. It was specifically mentioned that death occurred rather suddenly and unexpectedly in 4 cases. (No obvious cause for such a termination was found in the 3 necropsied cases from this group. All had fatty metamorphosis of the liver, but in only one case was the condition judged severe.)

LABORATORY AND ROENTGEN-RAY STUDIES. Hemoglobin values tended to run from normal to slightly high, reflecting frequent dehydration of this group. White blood cell counts obtained in 25 cases revealed elevations over 10,000 per c.mm. in 9 cases, all of whom showed some evidence of infection. Leukopenia (less than 5,000) appeared in 2 patients with pneumonia

and in one with cirrhosis and portal hypertension.

Liver function studies done on 9 cases were at least partially abnormal in all, most commonly showing reversal of albumin-globulin ratio and abnormal flocculation values.

Blood urea nitrogen values drawn shortly after admission frequently were low despite the usual dehydration, a finding which correlated well with the severe liver disease subsequently found in this group.

Serum electrolyte studies obtained in 8 cases showed no persistent abnormalities.

Blood cultures taken in 4 cases manifesting hyperthermia revealed probable contaminating organisms in 2 (*Micrococcus albus* and flavobacterium), and in the remaining 2 cases, 6 cultures showed no growth.

Chest roentgenograms were entirely normal in 2 of 11 cases so studied. Abnormalities included pulmonary tuberculosis (4), pneumonia (3), congestion (2), and bilateral unidentified upper lobe infiltration (1).

Electrocardiograms taken in 5 cases failed to reveal consistent abnormalities.

TREATMENT. An attempt was made to assess the adequacy of fluid replacement in accordance with modern concepts, using 2,000 to 2,500 ml. daily as the baseline requirement and adjusting for fever, for fluid losses through sweat and other means, and for increased activity and respiratory rates. It is our opinion that many of the severe cases require maintenance fluids totalling approximately 6 L. per day. Of the total of 39 fatal cases, only 10 received what was deemed adequate replacement; in another 10 the adequacy could not be accurately determined, and the remainder received insufficient fluids. Deficient fluid replacement was most frequent in the hyperthermic group. Two cases with heart and renal failure were believed to have received excess fluids and electrolytes.

Sedatives or tranquilizers were given in 32 of the 39 cases; the medication usually consisted of paraldehyde and barbiturates, alone or combined. Newer phenothiazine derivatives were given to only 4 patients because most of the deaths occurred prior to 1955. In some cases, large quantities of these agents were used, with relatively little benefit noted.

Two patients received ACTH. One transiently showed some improvement, but died rather unexpectedly the day after admission. No necropsy was obtained. The second patient was a severe cirrhotic in a state of hepatic coma. Three patients received corticosteroids. One had apparent benefit from intravenous hydrocortisone until this agent was stopped because of slight gastrointestinal hemorrhage. Shortly thereafter, an elevation of temperature occurred, with subsequent death. A second case received adrenocortical extract terminally without benefit; a third receiving this agent was a severe cirrhotic with bleeding esophageal varices.

All but 3 patients received vitamin B complex and vitamin C parenterally in large doses.

Twenty-eight patients received antibiotics or sulfonamides in full doses; in most cases, penicillin was used alone with little apparent effect.

POSTMORTEM FINDINGS (Table 2). While the myocardium was almost always abnormal, changes were usually mild and of a nonspecific nature, probably related in most instances to severe stress and fever. Hypertrophy was frequent and usually unexplained. Microscopic changes frequently consisted of fragmentation, loss of striations, patchy fibrosis, and edema. Congestive heart failure was not considered clinically

present in any of the cases ultimately receiving necropsies.

The lungs exhibited, to some extent, abnormalities in all cases; many of these abnormalities appeared to be terminal phenomena. The most common combination found was congestion, edema, and patchy bronchopneumonia; the latter was not sufficiently severe in the majority of cases to have accounted for the hyperthermia or fatal outcome.

The liver was uniformly abnormal; cirrhosis and fatty metamorphosis almost always were found alone or in combination. Cirrhosis was graded as severe in 5 instances, and fatty metamorphosis was considered severe in 9.

Another abnormality almost invariably appearing was cortical thinning and lipid depletion of the adrenal glands. In the only case noted to possess a normal gland, the patient died rather suddenly with severe bronchopneumonia 34 hours after admission. On microscopical examination, fewer than half of the cases showed what could be termed severe lipid depletion. Many exhibited only a minimal or moderate reduction of intracellular vacuoles even in the group manifesting hyperthermia and shock.

Except for congestion with or without edema, the brain generally was not remarkable on gross inspection. Unfortunately, microscopic sections were available for review in only 2 cases, one of which displayed a tendency toward reduction of and degenerative changes in ganglion cells, with dilated subarachnoid and perivascular spaces.

TABLE 2.—SUMMARY OF NECROPSY FINDINGS OBTAINED IN 27 CASES

HEART	
Normal	4
Dilation	12
Nonspecific degenerative changes	9
Left ventricular hypertrophy	9
Right ventricular hypertrophy	1
Patchy fibrosis	6
LIVER	
Normal	0
Fatty metamorphosis	18
Cirrhosis	17
Congestion	8
BRAIN	
Normal	0
Congestion	13
Congestion and edema	5
Atrophy	3
Cyst of third ventricle and aneurysm of ant. comm. art.	1
Subdural hemorrhage	1
LUNGS	
Normal	9
Congestion and edema with or without mild bronchopneumonia	18
Severe bronchopneumonia	5
Tuberculosis	3
Congestion alone	2
Intraalveolar hemorrhage	2
Peripheral emboli	2
Atelectasis	1
Emphysema	1
Lung abscess	1
ADRENAL CORTICES	
Normal	1
Lipid depletion	20
Focal hemorrhage	1
MISCELLANEOUS	
Gastritis	3
Dilatation of stomach	2
Diverticulosis of sigmoid colon with abscess formation	2
Esophageal varices	2
Duodenal ulcer	1
Duodenal ulcer with obstruction	1
Rupture of gallbladder with peritonitis	1
Acute renal tubular necrosis	1

The second of the 2 revealed merely increased intensity of staining of the myelinated fibers. Brain lesions in this disease have been reviewed extensively elsewhere (Bowman and Jellinek[4], Huber[18], Marchand[24], Tommasi[30]).

Other postmortem findings are listed in the miscellaneous column of Table 2. Of special interest is the finding of acute tubular necrosis in a patient suffering from acute renal shutdown. This patient suffered a tibial fracture with extensive contusion and tissue necrosis but also manifested hypotension after receiving phenothiazine drugs. Unsuspected severe unrelated abdominal disease sometimes appeared.

TABLE 3.—SUMMARY OF COMBINED MAJOR CLINICAL AND NECROPSY DIAGNOSTIC IMPRESSIONS IN THE FATAL GROUP

Fatty liver		21
Cirrhosis		19
Pneumonia		11
*Bronchopneumonia	9	
Lobar pneumonia	2	
Pulmonary tuberculosis		7
Peripheral neuropathy		5
Gastritis		3
Diverticulitis of sigmoid with pericolonic abscess		2
Duodenal ulcer		2
Bleeding esophageal varices		2
Intracranial trauma and hemorrhage		1
Hepatic coma		1
Acute renal tubular necrosis		1
Lung abscess		1
Erysipelas		1
Rupture of gallbladder with peritonitis		1

*Only cases believed to be clinically significant are included.

OVERALL STATISTICS. The mortality rate for the total period studied was 11.8%. Caucasians account for a significantly greater percentage (56%) of the patients in this series than is justified by their degree of representation in the overall hospital population (24%). The age difference between the averages of the surviving and fatal groups is highly significant, suggesting that advancing age adversely affects the prognosis. It is general knowledge that males dominate the group manifesting delirium tremens.

TABLE 5.—SUMMARY OF MAJOR CLINICAL IMPRESSIONS IN THE SURVIVORS. REPRESENTING 291 ADMISSIONS

Liver disease		53 (18%)
Pneumonia		43 (15%)
Bronchopneumonia	28	
Lobar pneumonia	9	
Unclassified pneumonia	6	
Convulsions		39 (13%)
Hyperthermia (Temp. 104° or more)		24 (8%)
Fractures		16 (5%)
Pulmonary tuberculosis		11 (4%)

From Table 5, one can see that the percentages of all major complications in the survivors is relatively low compared with those of the fatal group; but, by virtue of the differing criteria for diagnosis in the survivors, comparison of the two groups is difficult.

Mild to moderate temperature elevations were a common finding in all patients. However, the presence of hyperthermia (104° or more) definitely

TABLE 4.—GENERAL DATA OF ALL CASES

	Age			*Sex*		*Race*			
	Average	*SD*	*Range*	*M*	*F*	*Negro*	*White*	*Other*	*Total*
Fatal Cases	46.7 ±	10.0	23–72	34	5	11	28	0	39
Survivors	42.0 ±	10.5	19–72	251	40	139	151	1	291
Total	42.5 ±	10.4		285	45	150	179	1	330

is a bad prognostic sign regardless of etiology: Of the total 44 cases manifesting this sign, 20 (45.5%) died (Fig. 1).

Sixteen patients survived after having manifested hyperthermia unassociated with infection. It is of some importance that 4 of these patients received full doses of corticosteroids, and in all of this group, good hydration was eventually obtained. Hyperthermia was often present when dehydration was noted, whether on admission or following a period of poor fluid replacement in the hospital. When the fluid intake was increased, there usually was a prompt clinical improvement with a fall in temperature (See Case 2).

Among the 51 cases manifesting convulsions at the onset of or during the delirious state, 12 died (23.6%). This mortality rate is significant ($p = 0.0244$) when compared with patients not showing seizures and indicates a slightly poorer prognosis in the convulsing group.

Virtually all patients received some form of sedation. In earlier years, paraldehyde and barbiturates were popular. In recent years, the majority of patients have received phenothiazine derivatives (primarily promazine), frequently supplemented by barbiturates. The amount of these agents given seemed to play a secondary role in determining outcome. A total of 13 survivors received full doses of ACTH or corticosteroids (10 during the 1954-58 period).

The majority of deaths occurred dur-

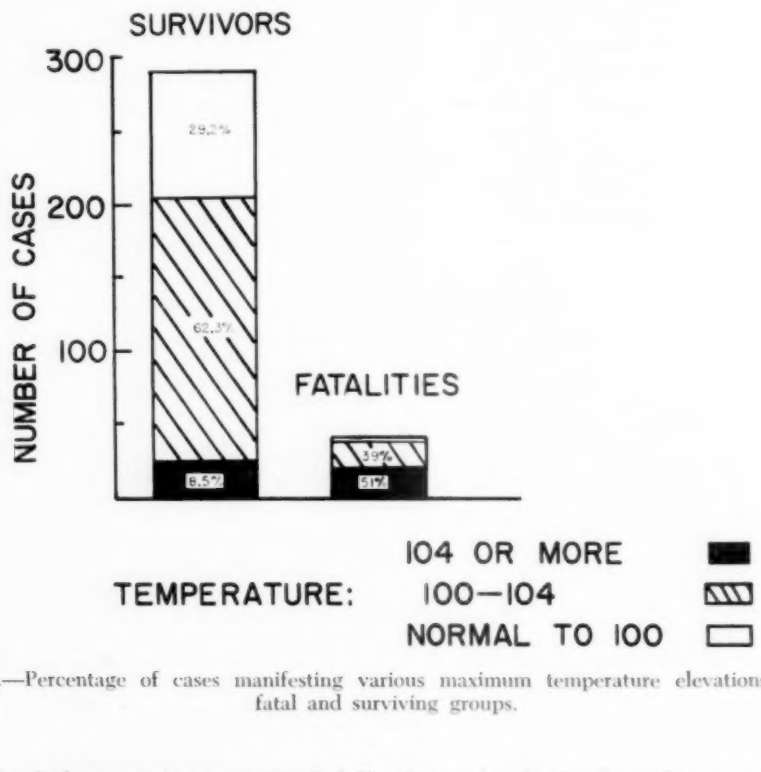

Fig. 1.—Percentage of cases manifesting various maximum temperature elevations in the fatal and surviving groups.

ing the 1950–54 period (Table 6), which indicates that a significant reduction in mortality rate occurred during the later years. There occurred a diminution both in the deaths related to major complications and in the deaths associated primarily with the delirious state (especially with hyperthermia). Undoubtedly, numerous factors contributed to this decline, but early recognition and treatment of complications plus better fluid replacement and supportive care seemed to be the most important determinants of survival.

TABLE 6

Time Period	*Total Cases*	*Fatalities*	*% Mortality*
1950–54	162	30	18.5%
1954–58	168	9	5.4%

It should also be noted in passing that, during the latter half of the study period, admission policy at Philadelphia General Hospital underwent a change: The percentage of delirium tremens cases admitted to medical wards increased from 29% to 45%, and the proportion of cases admitted to psychiatry and neurology wards declined from 49% to 33%.

Discussion. The present overall mortality rate of 11.8% serves to corroborate the fact that the mortality rate associated with delirium tremens has declined considerably during the past 50 years. The present rate may be compared with the figure of 37% reported from this institution in 1908 (Boston[5]). Because of our high complication rate and indigent patient load, our present mortality runs somewhat high in the spectrum reported recently from other institutions (2 to 16% range) (Cocheme[8], Gunne[16], Menzi[25], Thompson[29], Victor and Adams[32]). When patients succumb to delirium tremens in the absence of other major complicating diseases, the majority appear to do so 3 to 4 days after withdrawal symptoms have begun to appear. They become hyperthermic, hypermetabolic, and suffer huge fluid and electrolyte losses. In the remaining patients, complicating factors seem to play a large role in mortality. Of these complications, bronchopneumonia and liver disease are the most common.

Central nervous dysfunction probably largely accounts for hyperthermia in the absence of infection and may well play a large role in initiating a chain of events which culminates in pulmonary congestion, edema, and bronchopneumonia. Much difficulty has been encountered in attempting to define visible brain lesions and to denote them as the cause of delirium tremens. This difficulty is consistent with the impression that this disease arises from functional or biochemical rather than anatomic derangements of the central nervous system, although further investigation is necessary to elucidate this concept.

It has long been observed that fever could result from delirium tremens without the presence of complicating factors (Alzheimer[1]), but not until recently was it recognized that patients usually are dehydrated as a result of voluminous fluid and electrolyte losses (Bowman *et al.*[3], Brusa and DeMartis[7], Cohn[9], Godfrey, Kissen and Downs[14]). Increased motor activity also undoubtedly contributes heavily toward fluid loss and temperature elevation. At any rate, whatever the cause, when the stage of hyperthermia occurs, the prognosis is adversely affected (Brusa and DeMartis[7], Cocheme[8]). The hypovolemia resulting from dehydration probably accounts for the terminal picture of shock and coma. The entire process is well exemplified by the following 2 case summaries:

Case Reports. CASE 1. A 39-year-old white woman was admitted to neurological service on August 4, 1950, with a history of heavy alcoholism and having suffered a grand mal convulsion on the day prior to and on the morning of admission. On the morning of admission, confusion, tremors and an odor of alcohol on the breath were noted. The physical examination on admission revealed a confused, apprehensive, tremulous female who manifested slight cardiomegaly, hepatomegaly, and a hematoma over the occipital area. On the following day she became disoriented, hallucinatory, hyperkinetic, refused to take oral fluids, and manifested severe diaphoresis and intermittent vomiting. She received only 2,000 ml. of glucose in water by clysis during the last 48 hours of her life, and only small doses of phenobarbital intramuscularly. On the fourth hospital day her temperature rose to 104° rectally, and several hours later she entered a state of shock and expired. Necropsy revealed pulmonary congestion and edema with intraalveolar hemorrhage, mild fatty metamorphosis of the liver with congestion, moderate lipid depletion of the adrenal cortices, dilatation of the heart with patchy fibrosis microscopically, and passive congestion of the brain with diffuse atrophy.

CASE 2. A 36-year-old white woman was admitted in a slightly agitated state to the psychiatric ward on January 26, 1950, following an alcoholic binge. Just prior to admission, she had manifested a grand mal convulsion. The odor of alcohol was noted on her breath and there was slight hepatomegaly, but otherwise the physical examination was unremarkable. Within the next 24 hours she progressed to a full-blown state of delirium tremens with marked hyperactivity and diaphoresis. During the first 3 hospital days her total parenteral fluid intake was 1360 ml., and it was noted that her oral intake was poor. Her temperature gradually rose until on the fourth hospital day, when it was noted to be 107.4° rectally. At that time she was observed to be dehydrated, comatose, cyanotic, and in shock. She was immediately given 1500 ml. of plasma and 500 ml. of whole blood in rapid succession, followed by 4000 ml. of intravenous fluids within the next 24 hours. Shortly after this regimen had begun, she became normotensive and began to respond to stimuli. Tepid sponges were used to combat the temperature elevation. Her urinary output during this 24-hour period was 400 ml. On the following day, her blood urea nitrogen rose to 125 mg. per 100 ml., but subsequently returned to normal. During the next 4 days, she received an average of 5,600 ml. of fluids (including saline) daily intravenously with gradual improvement in her delirium. The temperature gradually fell, but did not reach normal until 2 weeks after its highest level was observed. Her sedation was limited to 800 mg. of barbiturates given during the 24-hour period when the temperature was at its highest level. She was discharged in good condition.

These cases serve to emphasize the need for careful fluid replacement and good supportive care, factors which appear to play a significant role in survival. In fact, our data suggest that careful attention to these factors can result not only in a reduction of mortality associated with severe hyperthermia, but also in the prevention of the development of the latter symptom. We are beginning to realize that delirium tremens frequently is a severe metabolic stress and should be managed on a medical ward (or any unit capable of handing such problems) in a way similar to the management of thyroid storm.

Of interest is the predominance of bronchopneumonia over the lobar variety. This situation probably can be attributed to both a reduced incidence of fatal lobar pneumonia in the present era and the fact that bronchopneumonia is more apt to occur in such debilitated patients suffering from convulsive seizures and other central nervous system derangements. It follows that careful attention to the respiratory tract is mandatory; frequent aspiration of the pharynx and trachea with induced coughing may prevent the occurrence of atelectasis and bronchopneumonia.

The relatively frequent finding of left ventricular hypertrophy and nonspecific myocardial changes probably resulted from combined factors. Hypertension often was suspected, but thiamin deficiency, as well as the recently described entity, alcoholic cardiomyopathy (Brigden[6]), also may have con-

tributed. Clinical congestive heart failure, however, was observed only rarely, but should be kept in mind during therapy.

Since the incidence of liver disease in delirium tremens is high in both fatal (Thompson[29]) and surviving (Kissin, Schenker and Schenker[21], Leevy, Patrylo and Doody[22]) groups, the role of hepatic abnormalities in relation to prognosis in delirium tremens is uncertain. The severity of liver involvement, however, may influence the prognosis unfavorably, as evidenced by the high incidence of severe disease in the present group of fatalities. One should, therefore, attempt to supply as much glucose and vitamins as is feasible, and if nutrition can be taken safely orally, protein should be supplied as well.

Occasionally a patient with delirium tremens manifests sudden death, a phenomenon which has been noted by others (Victor and Adams[32]) and causative mechanisms are obscure. Sudden death also has been observed in the absence of delirium tremens in association with fatty metamorphosis of the liver (Goldberg and Thompson[15]). This liver condition represents a common denominator in our cases and thus may have been the lethal force. Fat emboli from the liver to the lungs or brain may be fatal in such cases, since this process is said to occur with great frequency in alcoholics (Lynch, Raphael and Dixon[23]). However, it would appear more likely that we have yet to demonstrate the major cause of sudden death with delirium tremens. Heretofore unrecognized biochemical or electrolyte alterations are suggested possibilities.

There is little doubt that sedation plays a vital role in the treatment of these patients, both in reducing the stress and fluid requirements and in reducing the difficulty in ward management; but it should be kept in mind that their use is adjunctive and cannot replace good fluid and supportive management. In keeping with earlier evidence (Fraser *et al.*[13], Kalinowsky[20]), both paraldehyde and barbiturates appear to be desirable drugs, since they probably can substitute at least in part for the effect of alcohol on the central nervous system, thereby reducing the severity of withdrawal symptoms. However, in severe cases, these agents must be used in large quantities, not only because of the severity of the symptoms, but also so as to counteract the presumed cross-tolerance acquired to these agents through chronic alcohol addiction. Data extolling the virtues of phenothiazine derivatives are unconvincing and, in our experience, these agents are apt to fail when one needs them most. The phenothiazines also possess the further disadvantage of occasionally producing hypotension which is potentially harmful to this group, and they may not as effectively control convulsive episodes.

The administration of alcohol, while potentially efficacious, has marked disadvantages (Isbell *et al.*[19]), chief of which are its narrow margin of safety and its short duration of action.

Although it has been stated previously (Smith[27]) that in reality delirium tremens may be inextricably associated with adrenal cortical insufficiency, this hypothesis seems open to serious doubt. Even though alcoholics (particularly those with liver disease) do not respond as well as normals to ACTH stimulation, plasma levels of 17-hydroxycorticoids during delirum tremens appear to be significantly elevated (Kissin, Schenker and Shenker[21]). In almost all of our fatal cases, some degree of lipid depletion of the adrenals was found (an observation which has been noted previously [Hirsch[17]]). However, on microscopi-

cal examination, only a minority showed what could be termed severe lipid depletion. Our data suggest that, notwithstanding the facts above, corticosteroids seem to benefit these patients. This may be a nonspecific effect of these agents in reducing clinical severity; or conceivably there could be relative adrenal insufficiency in this disease. In the absence of more conclusive data concerning the relative value of these agents, our present policy is to administer parenteral hydrocortisone to delirious patients manifesting hyperthermia in the absence of underlying infection. Other situations require individualized decisions.

When to administer antibiotics is problematic, but it seems rational to use them only when infections are suspected. Severe hyperthermia *per se* is not necessarily evidence of infection, but it seems wise to use antibiotics when it occurs. This is particularly true when corticosteroids are being administered, since it is extremely difficult to rule out an infectious factor with the requisite speed and facility in this type of situation.

Much attention has centered recently on the role of magnesium in delirium tremens (Flink *et al.*[10-12]). However, even though magnesium deficiency frequently is a concomitant factor, it is not the cause of delirium tremens (Vallee, Wacker and Ulmer[31], Wacker and Vallee[33]). Since most of these patients have imbibed alcohol for prolonged periods with poor dietary intake and a high incidence of vomiting and diarrhea, one would expect the patients to be excellent candidates for both delirium tremens and a clinical syndrome secondary to magnesium depletion. In addition, some feel that magnesium therapy is of clinical benefit in delirium tremens (Flink *et al.*[10-12]), possibly because of its pharmacological effect. Therefore, it would appear rational to treat delirious patients with parenteral magnesium, particularly those who manifest tetany or convulsive seizures (Vallee, Wacker and Ulmer[31]).

Summary. Thirty-nine fatalities associated with delirium tremens in a 9-year period are reviewed and compared with survivors of this disease. Patients dying from this condition have a high rate of complications, most notable of which are pulmonary and liver diseases. A great number develop temperatures of 104° or greater in the absence of infectious causes, and many of these appear to die in a state of hypovolemia and vascular collapse. Current therapy is reviewed with the intention of finding means by which to prevent many of these mortalities. In this regard, we emphasize the importance of good supportive care and fluid replacement.

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SUMMARIO IN INTERLINGUA

Un Analyse Critic del Mortalitate Associate con Delirium Tremens Revista de 39 Mortes Occurrente Intra Novem Annos

Trenta-novem casos de morte occurrente in association con delirium tremens in un periodo de 9 annos es revistate e comparate con le casos de superviventes de ille morbo. Patientes qui mori ab iste condition ha un alte incidentia de complicationes. Le plus notabile tales es morbos pulmonar e hepatic. Un grande numero de iste patientes disveloppa temperaturas de 104 F o plus in le absentia de causas infectiose, e frequentemente illes pare morir in un stato de hypovolemia e de collapso vascular. Es presentate un revista del therapias in uso currente con le objectivo de trovar medios per que tal mortes pote esser evitate. In iste connexion nos sublinea le importantia de un bon regime supportative e le replaciamento de liquido.

SUMMARIO IN INTERLINGUA

(See page 30 for original article)

Sever Reaction a Sulfadimethoxina (Madribon)

Es describite le prime caso de un sever reaction a sulfadimethoxina. Vasculitis diffuse sequeva 7 dies de administration del droga. Le vasculitis esseva le plus prominente in le pelle e le renes: Sever dermatitis e critic insufficientia renal dominava le tableau clinic.

SEVERE REACTION TO SULFADIMETHOXINE (MADRIBON)

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The purpose of this report is to describe a serious reaction to sulfadimethoxine (Madribon) manifested by hypersensitivity vasculitis with erythema multiforme and renal failure. This represents the first report, so far as we are aware, of a serious complication attributed to this drug.

Case Report. S.S., a 59-year-old white housewife was admitted to Abington Memorial Hospital, October 9, 1959, with intractable headache and fever of 105° F. Her illness began October 6, 1959, with fever, headache and weakness. On the following day, a dry cough and backache developed.

Prior to the onset of the acute symptoms, she had received 1 gm. of sulfadimethoxine daily for 7 days for treatment of a chronic dermatosis of the fingers. No other local or systemic treatment was employed.

Past history indicated good health. An appendectomy and hysterectomy at age 40 was followed by an episode of acute urinary tract infection which apparently resolved completely with therapy. An extensive health survey at a diagnostic clinic in 1957 revealed no significant abnormalities. She had never experienced allergic disorders or drug reaction and was unaware of previous treatment with sulfonamid drugs. Her family history was noncontributory.

Physical examination upon admission revealed a temperature of 105.2° F., pulse 140 per minute, respirations 26 per minute and blood pressure 124/64. She was acutely ill, lethargic, moderately dehydrated and complained of severe headache. The principal finding was a rapidly evolving, macular, pinkish-purple rash over the trunk and extremities. The physical examination was otherwise negative. Within 12 hours, vesicles and pustules 3 to 5 mm. in diameter arose from erythematous or hemorrhagic bases involving almost the entire skin aud mucous membrane surface.

Initial laboratory data included a leukocyte count of 12,950 with 92% neutrophils. Hematocrit, BUN, CO_2, serum chloride, sodium, potassium, proteins, sedimentation rate and febrile agglutinins were reported within normal limits. Voided urine specimens contained many leukocytes and one plus albumin. Bedside chest roentgenographic examination demonstrated a density in the left lower lobe. Cultures of the blood and skin lesions were later reported sterile, and the spinal fluid was normal.

Initial therapy consisted of parenteral fluids and chloramphenicol. A dermatologic consultant on October 10, 1959, made a diagnosis of bullous erythema multiforme and advised steroid therapy with dexamethasone. The febrile course continued and as the urine volume progressively diminished the BUN rose. On October 14, the urine output was 190 ml. (BUN 65 mg. per 100 ml., CO_2 13 mEq. per L.) despite adequate hydration. The ratio of urine:serum urea concentration was 5, suggesting severe or irreversible renal damage (Perlmutter *et al.*[8]). Increasing renal insufficiency (BUN of 250 mg. per 100 ml.) with clinical deterioration led to the patient's transfer to Germantown Hospital on October 17, for dialysis.

Dialysis was carried out successfully on October 18, using Kolff's twin coil technique over a 6-hour period. Incident to dialysis, she was given 1,000 ml. of blood. The negligible urine output increased to 400 ml. on October 19 (BUN 116 mg. per 100 ml.) and the diuretic phase began October 21, with a urine output of 3,125 ml. (BUN 106 mg. per 100 ml.), reaching a peak on October 27, with an output of 8,810 ml. (BUN 60 mg. per 100 ml.).

The general picture before and after dialysis was one of critical illness with delirium, diarrhea, hematuria, cough, painful stomatitis, extensive dermatitis, fever and tachycardia. Chloramphenicol, supportive measures and intensive steroid therapy with hydrocortisone (400 mg. daily) were continued. Clinical improvement was slow and lagged behind the period of diuresis and laboratory improvement. Extensive laboratory investigation, including cultures of urine, sputum, stool, blood, skin and mouth for bacteria, yeast and fungi revealed no evidence of significant infection. A skin biopsy taken from a typical lesion of the back demonstrated nonspecific inflammatory reaction consistent with erythema multiforme.

Severe stomatitis necessitated parenteral fluids until November 1, 1959 (output 2,200 ml., BUN 42 mg. per 100 ml.). Hydrocortisone dosage was reduced, then changed to triamcinolone (32 mg. daily) prior to discharge on November 12, 1959. On November 18, 1959, she suffered a transient episode of right-sided aphasia and hemiplegia coincident with reduction of steroid dosage. There were no abnormal neurologic sequelae. Her subsequent course was uncomplicated. The skin lesions healed with some scarring. On May 10, 1960, the physical examination, urine analysis, BUN and sedimentation rate were normal and she has remained in good health.

Discussion. During the early era of sulfonamid usage, there were frequent reports of renal complications. Damage to the kidney was of two general types, that due to precipitation of crystals in the renal tubules and that associated with hypersensitivity reaction (Merrill[7]). Sulfadimethoxine is excreted as a highly soluble glucuronide (Koechlin, Kern and Engelberg[5]). There was no evidence that renal precipitation of the drug was a factor in this case. The erythema multiforme and multiple system involvement indicated a diffuse vasculitis with associated renal damage. Many of the earlier reported sulfonamid reactions demonstrated severe renal and skin involvement (French[3]) and more recently, Zeek[9] described fulminant renal damage characterizing the hypersensitivity form of vasculitis. Reports of erythema multiforme, some fatal, following sulfamethoxypyridazine (Kynex) have recently appeared (Cohlan[1], Craven[2], Garner[4], Lindsay *et al.*[6]).

There has been a recent resurgence of interest in sulfonamid drugs and although toxicity has apparently been greatly reduced, it would seem that any member of this drug family may induce serious reactions.

Summary. The first case of a severe reaction to sulfadimethoxine is described. Diffuse vasculitis followed a 7-day administration of this drug. The vasculitis was most prominent in the skin and kidneys since severe dermatitis and critical renal insufficiency dominated the clinical picture.

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(Interlingua on page 29)

REGIONAL ANTICOAGULATION DURING HEMODIALYSIS USING CITRATE*

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Active bleeding or a bleeding tendency has been considered a contraindication to hemodialysis, because of the necessity of administering anticoagulants during the procedure to prevent clot formation in the machine. Recently, this difficulty has been circumvented by the technique of regional extracorporeal anticoagulation wherein clotting time is prolonged in the blood in the artificial kidney, but not in the blood in the patient (Gordon *et al.*[4,5]). This state is attained by the infusion of heparin into the machine inflow, and the infusion of protamine into the machine outflow. It is the purpose of this paper to present a new method for achieving regional extracorporeal anticoagulation, using citrate. It is believed that this method has some advantages over the heparin protamine procedure; these will be discussed below.

Methods and Materials. The results of ten hemodialyses using citrate as an anticoagulant are reported. Six were performed on the Kolff-Brigham rotating drum machine; the remaining four on the commercially available disposable twin coil machine. All patients were adults and were hemodialyzed for renal failure. The dialyzing bath was made up in the usual manner (Mader and Iseri[10]), except that calcium was omitted in most of the trials. However, the tap water used had a calcium content ranging from 2.77 to 3.30 mg. per 100 ml. Baths were replaced after each 2 hours of dialysis.

Trisodium citrate · $2H_2O$, reagent grade, was made up as a 40% W/V solution in distilled water and prepared for parenteral administration by filtering through a fine ground glass filter and autoclaving in 100 ml. rubber-capped bottles at 121° C. for 15 minutes. During the latter part of the study, sodium dihydrogen citrate (containing 40 gm. citric acid per 100 ml.) was used. This was prepared by dissolving 438 gm. of reagent grade citric acid monohydrate in 700 ml. of distilled water, and by adding approximately 2.1 equivalents of sodium hydroxide. The solution was made up to one liter with distilled water. The final pH was approximately 3.8. After cooling and filtering through a fine ground glass filter, the solution was autoclaved in 300 ml. bottles.

Citrate solutions were infused into the blood intake of the artificial kidney, using a Sigmamotor pump T-8, which was modified by a gear box between the speed changer and the pump proper to produce a four-fold

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reduction in the speed of the final drive shaft (Fig. 1). Tygon tubing with a 1/16" I.D. and a 3/16" O.D. was autoclaved and used in the pump. The rate of infusion of the monosodium citrate solution was monitored by a sterilized buret connected by a three-way stopcock to the system, and ranged from 0.5 to 0.7 ml. per min., corresponding to 200 to 280 mg. of citric acid per minute. Blood flow through the artificial kidney ranged from 200 to 375 ml. per minute.

Clotting times were determined on blood issuing from the radial artery at a point before the admixture of citrate (referred to as arterial blood) and on the blood leaving the machine (referred to as venous blood).

Plasma sodium was determined on heparinized blood, using the Beckman flame photometer (Mosher *et al.*[13]). Blood was collected under oil for total carbon dioxide content, using the volumetric Van Slyke method (Van Slyke and Stadie[20]), and for pH, using the

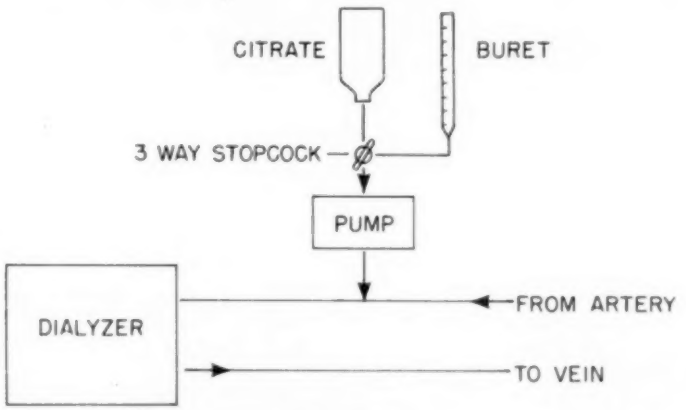

Fig. 1.—Diagram of arrangement for using citrate as a regional anticoagulant. Explanation in text.

Citrate determinations on heparinized plasma and dialyzing fluid were carried out by the method of Ettinger, Goldbaum and Smith.[2]. Calcium determinations were made by the chloranilic acid method of Ferro and Ham[3]. Plasma was digested by a nitric acid-perchloric acid mixture, and the residue neutralized with dilute ammonium hydroxide before precipitating the calcium. All these determinations were performed in duplicate.

Clotting time was determined by placing 1.0 ml. of whole blood, collected in an unsiliconized syringe, in a test tube of 11 mm. diameter containing 0.1 ml. of saline. Clotting time obtained by percutaneous venipuncture on untreated uremic subjects was performed on the blood collected in the second syringe, 5 ml. in the initial syringe having been discarded. Clotting times obtained on patients undergoing dialyses were done on samples obtained by simple puncture of rubber-sleeved plastic tubing. The tube was kept at room temperature and inverted periodically. The end point was taken as that time when no flow occurred with complete inversion. Beckman pH meter with an anaerobic micro electrode. The pCO_2 was calculated using a pK_1 of 6.10 and a factor of 0.0301 mM. per mm. Hg (Peters and Van Slyke[15]). Plasma urea nitrogen was determined by the diacetyl monoxime method (Marsh, Fingerhut and Kirsch[11]).

Results. CLOTTING TIMES. The mean clotting time of 6 chronic uremic patients not undergoing dialysis was 10.3 ± 2.4° min. Pre-dialysis clotting times were not obtained, but those determined during hemodialysis are shown in Fig. 2. The shaded area indicates the normal range (mean plus and minus two standard deviations) for chronically uremic subjects referred to above. The mean clotting time of the patients' arterial blood entering the machine was 11.4 ± 3.0° minutes, which was not significantly different

from the mean of the untreated uremic group ($p>0.4$). In 22 instances, the clotting time of the machine inflow (arterial) blood was done in the usual manner and also with the addition of 0.1 mg. calcium per 1.0 ml. of blood. There was no difference in the clotting time in the two groups, the means being respectively, 12.3 ± 3.8* minutes and 12.2 ± 3.5* minutes.

The clotting times of the blood leaving the machine are plotted in Fig. 2. The mean of these values was 24 ± 11* minutes. Despite the fact that 14 of the 67 determinations revealed clotting times within the range of normal for uremic subjects, no significant clot formation occurred in the extracorporeal circulation.

On two occasions necessitating cessation of blood flow through the machine for 10 minutes, the citrate infusion was stopped, and the dialyzing membrane removed from contact with the bath. No clots were evident on restarting the dialysis. In several instances, a clot formed at the site of entry of the citrate solution into the blood stream. In no case did this clot interfere with the procedure.

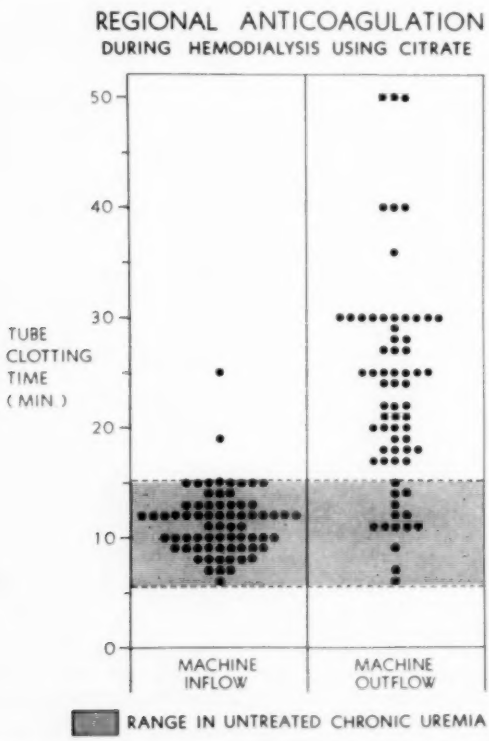

Fig. 2.—Clotting time obtained during 10 hemodialyses, using citrate as a regional anticoagulant.

CITRATE (Fig. 3). The plasma citrate level of the arterial blood prior to dialysis ranged from 15 to 139 μg. per ml. The four highest figures were from the

*Standard deviation.

initial dialyses, in which the sample was not drawn until approximately a minute had elapsed after the machine had been started. Excluding these samples, because of probable admixture of citrated bank blood which was used to prime the machine, the mean arterial plasma citrate level was 37.1 when either blood or citrate flow was changed markedly.

Venous blood drawn from 4 patients 17 hours following dialysis had a mean citrate level of 22.2 μg. per ml., with a range of 16 to 30 μg. per ml. In one patient having an arterial plasma citrate level of 167 μg. per ml. just before

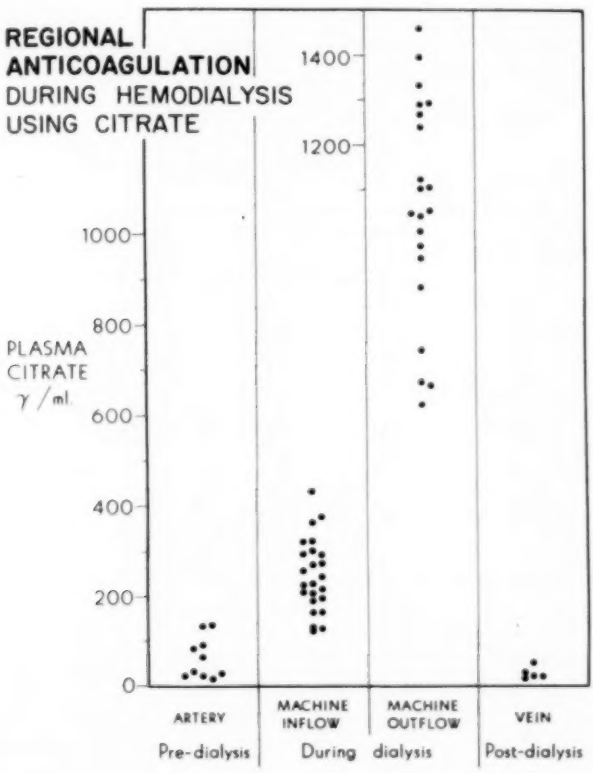

Fig. 3.—Plasma citrate levels during 10 hemodialyses, using citrate as a regional anticoagulant.

± 10.6* μg. per ml. The mean citrate level of the arterial plasma during dialysis was 252 ± 81* μg. per ml.; the mean for the plasma returning from the machine to the patient was 971 ± 243* μg. per ml. Both arterial and venous levels remained relatively constant during the dialyses, except

termination of dialysis, the venous plasma citrate level had dropped to 52 μg. per ml. 80 minutes after the end of the procedure.

The total amount of citrate infused and the amount removed by dialysis during each treatment are shown in Table 1. The difference between these

two figures, representing the citrate retained by the patient, is also shown. In the entire group for each 2-hour period of dialysis, a mean of 29.4 ± 6.1* gm. of citrate was infused; 9.7 ± 2.2* gm. were dialyzed out; and a mean of 19.6 ± 5.5* gm. was retained.

REGULATION OF CLOTTING TIME. Preliminary *in vitro* tests indicated that over 800 μg. of citric acid per ml. of plasma were required to prolong the clotting time. Subsequent experience made to keep the venous clotting time over 15 minutes; a fall below this level dictated an increase in the rate of citrate infusion. However, in a few instances, the maintenance of venous clotting times under 15 minutes for an hour or so did not result in clot formation. An excessive prolongation to over 30 minutes usually called for a reduction in the rate of citrate infusion, although it was not considered to be detrimental unless the arterial clotting

TABLE 1.—EXTERNAL EXCHANGES OF CITRATE

			Citrate Removed by Dialysis Citric Acid (gm.)				
Dialysis	*Duration Dialysis (Hours)*	*Total Citrate Infused/ Dialysis Citric Acid (gm.)*	*Bath 1 (0–2nd hours)*	*Bath 2 (2nd–4th hours)*	*Bath 3 (4th–6th hours)*	*Total*	*Citrate Retained by Patient During Dialysis (Citric Acid gm.)*
1	4	54.8	8.4	8.2		16.6	38.2
2	4	49.1	10.4	12.4		22.8	26.3
3	6	112.8	11.7	11.7	9.8	33.2	79.6
4	4	36.4	9.2	6.9		16.1	20.3
5	5	59.8	*	6.9	*	*	*
6	6	97.7	12.0	13.3	13.5	38.8	58.9
7	4	67.2	11.8	9.1		20.9	46.3
8	6	96.8	9.4	8.7	8.8	26.9	69.9
9	6	91.8	*	*	*	*	*
10	4	57.6	7.2	5.2		12.4	45.2

*Not determined

during the dialyses supported this finding. On the occasions when venous clotting time was not prolonged, venous citrate level was less than 800 μg. per 100 ml. of plasma. To attain this level of citrate at the machine outflow, the rate of citrate infusion had to be 0.5 ml. per min. for a blood flow of about 200 to 250 ml. per min. Higher rates of citrate infusion, up to 0.7 ml. per min., were used for blood flows of 300 to 375 ml. per min. Arterial and venous clotting times were determined at least once every hour and adjustments made in citrate flow on the basis of the venous clotting time. An effort was time also increased to over 15 minutes.

CALCIUM (Table 2). In the first eight dialyses reported, no calcium was added to the bath; the calcium concentration of the dialyzing fluid was that of the tap water used and ranged from 2.77 to 3.30 mg. per 100 ml. In these runs, there was a net loss of calcium from the patient, as indicated by a rising calcium concentration in the dialyzing fluid and a falling concentration in the plasma as it coursed through the machine. An exception was Case 5 in whom initial plasma calcium level was only 5.8 mg. per 100 ml. Furthermore, there was a small gradual

*Standard deviation.

fall in the arterial plasma calcium concentration during the procedure. In the initial eight runs, the total loss of calcium per dialysis, as calculated from bath concentration changes, ranged from 0.19 to 0.68 gm.

In the last two dialyses, the bath was prepared with an initial calcium concentration of about 5 mg. per 100 ml. In these cases, there was a rise in the arterial plasma calcium concentration during the procedure, as well as a rise in the calcium concentration of the plasma as it coursed through the machine. In the one case where bath calcium changes were measured, there was a net gain of 0.24 gm. of calcium by the patient during the procedure. In several cases not detailed here, the raising of bath calcium to 5 mg. per 100 ml. seemed to increase the requirement of infused citrate in order to attain adequate anticoagulation.

IONIZED CALCIUM. Neither ultrafilterable nor ionized calcium was determined in this study. However, twitching, carpopedal spasm, a positive Chvostek sign, and convulsions did not appear in these patients. Serial electrocardiograms were taken to monitor the cardiac manifestations of a possible significant decrease in ionized calcium. The Q-T interval was measured in Standard lead II, expressed as QT_c (Taran and Szilagyi[19]) and plotted (Fig. 4). It can be seen that no consistent change occurred during dialysis. No cardiac arrhythmias were encountered.

OTHER ELECTROLYTE CHANGES. In the first three dialyses, citrate was infused as the trisodium salt. Inordinate elevations of arterial plasma sodium were found at the end of dialysis (149, 154, 149 mEq. per L., Table 3). In the subsequent runs, monosodium dihydrogen citrate was used, resulting in less marked elevations of plasma sodium at the end of the procedure.

The infusion of this acidic citrate solution (pH approximately 3.8) into the circuit caused the blood pH just beyond the point of infusion to fall to rather low levels, being 6.97, 6.88, and 6.70 units in the three instances where measurements were made. The pH of the blood leaving the artificial kidney was 7.21 ± 0.12°, and that of the

TABLE 2.—CHANGES IN CALCIUM

Dialysis No.	Duration Dialysis (Hours)	Plasma Calcium (mg./100 ml.) Hours of Dialysis 0	2 A	2 V	4 A	4 V	6 A	6 V	Bath Calcium at Start mg./100 ml.	Total Calcium Removed gm.
1	4	7.6	7.5	5.6	7.5	6.1			2.90	0.19
2	4	8.2	8.7	7.4	8.0	7.3			3.30	0.25
3	6	8.0	7.9	7.5	7.6	6.7	7.5	6.8	2.77	0.51
4	4	5.8	5.8	5.9	6.3	6.2			2.86	0.32
5	5	9.1	8.4	7.9	7.6	7.1	7.5+	7.3+	3.07	*
6	6	10.2	9.5	9.0	9.0	8.6	9.0	7.9	2.92	0.68
7	4	8.3	8.0	7.5	7.6	7.3			2.89	0.28
8	6	8.5	8.8	8.1	8.0	7.7	8.1	7.7	*	*
9	6	7.1	7.6	8.2	7.8	8.4	8.4	*	5.01	*
10	4	7.9	8.1	8.3	8.1	8.1			5.32	−0.24#

A = Machine inflow. V = Machine outflow. +After 5 hr. of dialysis. *Not determined. #Calcium gained by patient.

arterial blood averaged 7.57 ± 0.08°, all determinations having been made after 2 to 6 hours of dialysis. The low pH of the blood leaving the machine was due to a high pCO_2, and the high pH of the arterial blood was due to a low pCO_2 (Table 3).

Total arterial plasma carbon dioxide content and bicarbonate levels rose to normal or near normal levels during

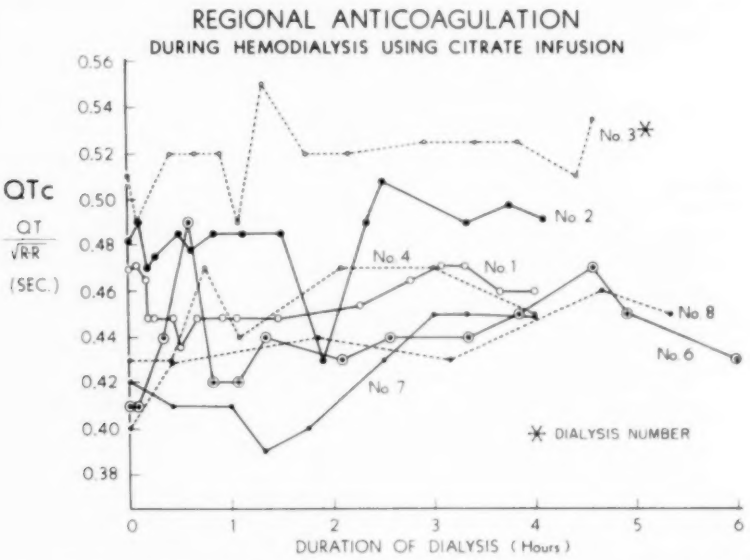

Fig. 4.—Serial changes in the QT_c of the electrocardiogram during hemodialyses, using citrate as a regional anticoagulant.

the procedure in every case, despite the acidic nature of the infused citrate (Table 3).

Discussion. With the present method, a differential in clotting time was established between the intra- and extracorporeal portions of the circulation. The clotting time of the machine portion of the circuit was sufficiently prolonged to allow successful dialyses. The clot which formed at the point of entry of the concentrated citrate solution into the blood stream was never a detriment to successful dialysis. Its genesis may lie in mechanical factors such as turbulence and the presence of the citrate carrying needle in the blood stream, or in the prothrombin activating effect of concentrated citrate solutions (Seegers[18]). The mean arterial clotting time, representing the state of the blood in the body, was not prolonged. It was not likely that a decrease in ionized calcium sufficient to affect the clotting time of the arterial blood existed, since the *in vitro* addition of calcium in great excess (0.1 mg. per 1.0 ml. of blood) did not shorten the clotting time. Although a normal clotting time does not exclude a tendency to bleed, it would seem to indicate a safer state than the prolongation of clotting time in the entire circuit.

The differential in clotting time in the two portions of the circuit can be attributed to the difference in citrate concentrations between these same regions. The high plasma levels in the

TABLE 3.—ACID BASE CHANGES

Dialysis	Duration (Hrs.)		Sodium mEq./L.				pH				CO_2 Content mM./L.				Calculated Plasma HCO_3 mEq./L.				Calculated pCO_2 mm.Hg				Plasma Urea Nitrogen mg./100 ml.	
			0 hr.	2	4	6	0 hr.	2	4	6	0 hr.	2	4	6	0 hr.	2	4	6	0 hr.	2	4	6	Start	End
1	4	A	144		149						21.9		28.6										156	75
		V																						
2	4	A	149		154						21.4		35.3										159	65
		V																						
3	6	A	143			149					10.7			32.6									288	86
		V																						
4	4	A	140		149			7.58	7.62		25.9	25.9	26.3			25.1	25.4			27	28		198	96
		V						7.40	7.45			25.9	26 3			24.7	25.2			38	35			
5	5	A	137	149	150	149*		7.60															172	88*
		V		158	160	150*		7.42																
6	6	A	131	140	146	144		7.47	7.70	7.55	11.6	17.9	21.9	24.6		17.2	21.4	23.8		23	16	27	370	153
		V		149	155			7.10	7.20	7.15		21.9	24.6	25.9		19.9	22 8	23.8		64	58	69		
7	4	A	138		143			7.55			23.2	26.3	29.9			25.4				29			270	126
		V						7.22				25.9				23.1				57				
8	6	A	133	136	140	142	7.38	7.60	7.52	7.65		26.3	21.9			25.5	21.1			26	26		168	80
		V		142	150			7.30	7.30	7.31		19.7	19.6			18.5	18.4			37	37			
9	6	A	140	140	142	140	7.35	7.58	7.65	7.62	22.3	29.0	28.2	31 2	21.1	28.1	27.3	30.3	38	30	24	29	350	198
		V		142	142			7.30	7.42			27.6	26.3			26.0	25.1			53	38			
10	4	A	137	140	142			7.45	7.58		13.8	19.2	27.6			18.4	26.7			26	28		150	78
		V		145	148			7.00	7.15			20.0	23 6			17.8	21.7			70	61			

A = Machine inflow

V = Machine outflow

*5 hours

machine, averaging 971 μg. per ml. at the outflow, were maintained by the infusion of citrate at the machine inflow. The relatively low arterial values were due to the uptake of citrate by the body tissues. The constancy of the arterial citrate levels during the dialyses suggested that the rate of utilization of citrate was not exceeded by the rate of infusion. Furthermore, a rapid fall in citrate levels was noted after termination of the infusion, a phenomenon noted by Howland *et al.*[8] in citrate infusion experiments.

Plasma may be cleared of citric acid by metabolic processes (chiefly oxidation), by urinary excretion (Herndon and Freeman[7]), or by uptake by bone. The net utilization by bone is of relatively small magnitude (Cortese and Kuyper[1]), and, in these patients, the second factor is probably also very small. Oxidation, then, appears to be the chief means of removal of citric acid in these subjects, and appears to account for the maintenance of relatively low values of arterial citrate. In dogs, the kidneys are responsible for the oxidation of much of infused citrate (Herndon and Freeman[7]). However, in the subjects of the present study, all of whom had advanced renal insufficiency, it seems likely that most of the infused citrate was metabolized in tissues other than the kidney since the availability of citrate to the kidneys must have been sharply limited by a very low rate of renal blood flow.

The mean arterial citrate level of 252 μg. per ml., although lower than the extracorporeal concentrations, was elevated when compared to the predialysis mean of 37 μg. per ml. It was also higher than the median plasma citrate level of 48.9 μg. per ml. (range 14 to 150 μg. per ml.) in patients with renal failure, reported by Pierce, Guild and Merrill[16], and the mean of 12.0 ± 1.3* μg. per ml. in acute renal failure reported by Nordmann, Marty and Nordmann[14]. Nordmann used the method of McArdle[12] in obtaining this low figure; he felt that the method of Ettinger, Goldbaum and Smith[2], used in this study and in that by Pierce, gave falsely high results due to the inclusion of other plasma organic acids present in increased amounts in uremia. However, it was felt that this nonspecificity did not affect the present results significantly because of the large amounts of exogenous citrate involved. The question, then, of the possible harm of arterial citrate levels of 100 to 400 μg. per ml. attained in these experiments must be raised.

Calculations based on the $pK_{Ca\ cit.}$ of 3.22 (Hastings *et al.*[6]) would suggest that, at a total plasma calcium level of 8 mg. per 100 ml. and a citrate level of 252 μg. per ml., about 4 mg. per 100 ml. of calcium would be tied up as citrate, compared to the 0.5 mg. per 100 ml. or so estimated to be tied up by citrate in normal plasma. Despite this, no overt evidence of tetany was noted. No consistent prolongation of the QT interval was found. The known antagonistic effect of calcium upon the cardiotoxic effect of hyperpotassemia (Winkler, Hoff and Smith[22]) raised the question of the safety of infusing citrate into a subject with electrocardiographic evidence of potassium intoxication. In one of the present subjects, evidence of moderately severe potassium intoxication was present on the electrocardiogram before dialysis. With the onset of dialysis, the electrocardiographic changes of potassium intoxication gradually disappeared in the usual manner.

Howland *et al.*[8] infused citric acid into adults at a rate of 8.6 mg. per kg. body weight per minute, reaching a peak plasma level of 796 μg. per ml.

*Standard deviation.

There was a prolongation of the QT interval, but no tetany was noted. Krautwold and Dorow[9] infused up to 6.0 gm. of citric acid in 4 minutes into 25 conscious human volunteers and noted tetany, a prolongation of QTc, and clouding of consciousness. The rate of infusion of citric acid in the present study did not exceed 0.33 gm. per minute. Since the rate of citrate removal by the machine was at least 0.04 gm. per minute, the net rate of citrate infusion was never over 0.29 gm. per minute.

Another undesirable effect of citrate infusion in animals has been the excessive urinary loss of calcium (Rose[17]). Although urinary calcium excretion was not measured, the limited duration of the citrate infusion, as well as the marked oliguria present in most of our subjects made any excessive urinary calcium loss unlikely.

In those runs where initial bath calcium was kept about 3 mg. per 100 ml., calcium was lost through the machine, ranging from 0.10 to 0.68 gm. per dialysis. The experience in dialyses nine and ten suggested that elevation of bath calcium to the level of 5 mg. per 100 ml. would eliminate this loss. However, further experience has shown that the requirement for citrate is thereby raised. Our present operating plan calls for no supplementation of calcium in the bath.

The use of trisodium salt of citric acid in the first three runs resulted in very high arterial plasma sodium levels at the termination of the procedure, since about 1,400 mEq. of sodium were infused per 6 hours of dialysis. For this reason, NaH_2 citrate was used in subsequent dialyses. This resulted in lower terminal plasma sodium levels, but because of the low pH (about 3.8) and the amount of free citric acid (about 1,000 mEq. per 6-hour run) infused, the question of disturbances in acid-base balance arose. This mixture did indeed tax the buffers of the blood into which it was infused, lowering the pH to about 6.8. This was a temporary condition, lasting only until the dialyzing membrane was reached. Here the buffers were restored so that at the machine exit, the plasma bicarbonate level had risen significantly, and the pH had risen to about 7.2. A further increase in pH was prohibited by the high pCO_2 value of the blood leaving the machine, this being due to the 10% CO_2, 90% O_2 atmosphere in the artificial kidney. The respiratory alkalosis noted in the patients' blood during and after dialyses has been noted previously (Weller, Swan and Merrill[21]) in runs not using citrate, and is attributed to continuing hyperventilation. The rise in the patient's plasma bicarbonate in these runs was of the same magnitude as that in heparin anticoagulated dialyses (Weller, Swan and Merrill[21]).

The chief advantage of citrate over heparin is that it requires no antidote. The need for protamine with heparin leads to the necessity for accurate titration of one agent against the other, a procedure which calls for careful attention and the use of fairly large volumes of solution. The present method requires, at most, the infusion of 250 ml. of solution during a 6-hour run and demands the careful control of the rate of entry of only one solution. The anticoagulant, furthermore, is metabolized in the body as a source of energy. Its end products are sodium bicarbonate (and carbon dioxide and water), which can well be utilized by patients in renal failure.

Summary. A method for producing extracorporeal regional anticoagulation during hemodialysis has been described. Sodium dihydrogen citrate containing 40 gm. of citric acid per 100 ml. was infused into the blood

going from the patient to the artificial kidney at a rate ranging from 200 to 280 mg. of citric acid per minute. This produced a citrate level in the plasma leaving the machine of 971 ± 243* μg. per ml. Due to rapid utilization by the body, citrate level in the patient's arterial blood was lower, having a mean value of 252 ± 81* μg. per ml. Corresponding clotting times averaged 24 ± 11* minutes and 11.4 ± 3.0* minutes. The latter figure matches closely the clotting time (10.3 ± 2.4* minutes) of blood from uremic patients not undergoing hemodialysis or receiving anticoagulants. The dialyzing bath contained only 3 mg. per 100 ml. of calcium, but was otherwise of the usual composition. Neither tetany nor serious disturbances of hydrogen ion and electrolyte concentrations occurred. In 10 hemodialyses, successful regional anticoaglation was obtained, as measured by whole blood clotting times, and evidenced by the absence of bleeding by the patient and absence of significant clot formation in the machine.

*Standard deviation.

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SUMMARIO IN INTERLINGUA

Anticoagulation Regional per Medio de Citrato Durante le Hemodialyse

Es describite un technica de producer extracorporee anticoagulation regional durante le hemodialyse. Citrato dihydrogenate de natrium continente 40 g de

acido citric per 100 ml esseva infundite in le sanguine fluente ab le patiente verso le ren artificial con un velocitate de inter 200 e 280 mg per minuta. Isto produceva in le plasma al exito ab le machina un nivello de citrato de 971 ± 243 (D.S.) μg/ml. A causa del utilisation rapide per le corpore le nivello de citrato in le sanguine arterial del patiente esseva plus basse, amontante a un valor medie de 252 ± 81 μg/ml. Le correspondente tempores de coagulation habeva valores medie de 24 ± 11 minutas e 11,4 ± 3,0 minutas. Le secunde de iste valores es multo similar al tempore de coagulation (10,3 ± 2,4 minutas) de sanguine ab patientes uremic non sub hemodialyse e non recipiente anticoagulantes. Le banio de dialyse contineva solmente 3 mg per 100 ml de calcium sed habeva alteremente le composition usual. Ni tetania ni grave disturbationes del concentrationes de iones de hydrogeno o del electrolytos ha occurrite. In 10 hemodialyses successose anticoagulation regional esseva obtenite, a judicar per mesurationes del tempores de coagulation de sanguine total, le absentia de sanguination in le patiente, e le absentia de significative formation de coagulo in le machina.

TETANUS IN AN URBAN COMMUNITY

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This is a report of 9 cases of tetanus personally observed in an urban community during an 8-year period. It is prompted because a recent suggestion that penicillin might protect against tetanus was not borne out in this series, since 2 of the patients, who received this antibiotic soon after injury, died of tetanus (Filler and Ellerbeck[5]).

Recent publications regarding tetanus might lead one to believe that this disease is now seen almost exclusively in large municipal hospitals in patients of dubious social habits or in more remote rural areas (Altemeier, Culbertson and Gonzales[2], Axnick and Alexander[3]). This small series will point out that it still may be seen in all segments of the population by physicians in a private metropolitan practice.

Case Reports. CASE 1. The patient was a 15-year-old boy who was transferred from one hospital to another for reduction of a compound fracture of the left forearm. It was incorrectly assumed at the second hospital that tetanus antitoxin had been given at the first. Three hundred thousand units of procaine penicillin were given at the second hospital 12 hours after injury, and the puncture wound, where the bone had been exposed, was cleaned thoroughly and dressed. Five days after injury, the patient complained of numbness of the fingers and 2 days later generalized tetanus began.

During the next 24 hours, 600,000 units of tetanus antitoxin and 20,000,000 units of penicillin were administered. The wound was excised and drained and antitoxin (40,000 units) was instilled into the area of the wound. A tracheostomy was performed and the patient was sedated with Sodium Amytal, which was required in large doses for the control of severe generalized tetanus. On the twelfth hospital day, apnea occurred, probably due to an overdose of Sodium Amytal, and he was placed in a respirator and treated with picrotoxin. On the thirteenth hospital day, spontaneous breathing was re-established. At this time, opisthotonos was so severe that the tension exerted on the abdominal skin caused the skin to separate. The patient died 14 days after his accident. Postmortem examination revealed bronchopneumonia and atelectasis.

Tissues from the fracture site were removed and suspended in saline. One milliliter of this suspension was injected intraperitoneally into a guinea pig which died with generalized tetanic convulsions within 20 minutes.

CASE 2. The patient was a 24-year-old Negro housewife who was admitted to the Milwaukee County General Hospital with stiff neck and severe trismus. She had suffered a small puncture wound of the wrist, while gardening, one week earlier. Five days before admission, she had received an injection of penicillin and a "tetanus shot" from a private physician (it is not certain how much penicillin she received and the tetanus shot was assumed to have been toxoid). In the hospital, the patient maintained an almost constant board-like rigidity of the abdomen, even though Sodium Amytal and 100,000 units of antitoxin were given intravenously and 300,000 units of penicillin and 100 mg.

of diphenhydramine hydrochloride were given intramuscularly. Six hours after admission, she suddenly became apneic and cyanotic. She was revived with artificial respiration, but stopped breathing again during an attempt at endotracheal intubation. Vigorous attempts at resuscitation were unsuccessful.

CASE 3. The patient was a 19-year-old drill press apprentice who had suffered numerous lacerations in his attempts to learn his trade. Following 2 days of difficulty in opening his mouth and chewing, he was admitted to the hospital with true "lockjaw." History revealed that he had received tetanus antitoxin on 2 occasions several years before, but that he had never been immunized. His skin test was positive, so that it was deemed necessary to desensitize him prior to the administration of full dosage of antitoxin. This was done by doubling an initial subcutaneous dose of 10 units of antitoxin (0.1 mm. of the 1:5,000 dilution) every 20 minutes until a total of 12,070 units had been given. Then 4 ml. of undiluted antitoxin was given intramuscularly every 2 hours until a total of 16,000 units was given (Murphy[7]). During the time required for the administration of the antitoxin, tetanus progressed to the point of severe generalized tetanic seizures which were controlled by large doses of Sodium Amytal and sodium phenobarbital given intravenously and Mydnesin given orally.

Each day that the patient was febrile, he received 1 gm. of chloramphenicol and 1,000,000 units of penicillin intravenously. Feeding was accomplished by stomach tube for a 6-day period of severe generalized tetanic contractions. While a tracheostomy set was held ready, its use was not required since the patient seemed able to handle his secretions very well.

The tetanus continued in spasmodic form for 16 days, but after the sixth day there was a gradual decrease in intensity which allowed a concomitant reduction in the amount of sedation necessary for the patient's comfort.

CASE 4. The patient was an 87-year-old white woman who was admitted to Mt. Sinai Hospital with complaints of stiff neck and inability to swallow. Examination revealed frank "lockjaw" and generalized tetanus. There was a reddened area on her leg which had been penetrated by a sliver 10 days before admission. Two hundred forty thousand units of tetanus antitoxin and 2,000,000 units of penicillin were administered intravenously during the first 12 hours in the hospital. The wound on her leg was drained of 1 ml. of frank pus and the area was infiltrated with 10,000 units of antitoxin. Sedation was accomplished with sodium phenobarbital intramuscularly and mephenesin (Mydnesin) orally. There was moderate improvement up to the third hospital day; then she had a generalized tetanic convulsion that necessitated intravenous Sodium Amytal for control. She never fully regained consciousness after this and died on the sixth hospital day.

It was our opinion that death was due to cerebral hemorrhage that occurred during the severe tetanic convulsion. A tracheostomy had not been done.

Postmortem examination (on all but the head) did not reveal the cause of death.

CASE 5. The patient was a 35-year-old Caucasian farmer who was brought to the Milwaukee County Hospital by the police who had found him lying unconscious in an open field. He had generalized tetanus and "lockjaw." No clear-cut history of injury was obtained. An emergency tracheostomy was performed, and 10,000,000 units of penicillin and 60,000 units of antitoxin were given intravenously. Sodium Amytal was added to the continually running infusion to control the generalized seizures. Feeding was accomplished by stomach tube. When signs of bronchopneumonia developed, chloramphenicol was administered intramuscularly with seemingly good results. A drug rash appeared on the fourth hospital day and this was treated with corticotropic hormone. For 18 days, the patient continued to have generalized convulsions which were controlled with Sodium Amytal. Then rapid improvement ensued. His tracheostomy tube was removed on the twenty-third hospital day. The patient was discharged from the hospital, well, on the thirtieth hospital day.

CASE 6. The patient was a 15-year-old white boy who was admitted to Milwaukee County Hospital because of "lockjaw." He had been having mild stiffness of the neck for one week and remembered having been scratched by a dog "a few weeks previously." Examination revealed trismus of the jaw. A generalized tetanic seizure was produced by the slightest stimulus. Intravenous administration of 100,000 units of tetanus antitoxin, 200,000 units of penicillin and Sodium Amytal was begun immediately. The manifestations of tetanus returned each time the amount of Sodium Amytal was decreased during the next 3 days; but, from the fourth through the tenth hospital day, the tetanus subsided and oral feeding became possible. All treatment was discontinued on the tenth

TABLE 1.—SUMMARY OF CASES

Name	Case No.	Prev. Imm. (Active)	Age	Sex	Race	Occupation	Incubation Period Days	Passive Immunity	Tracheotomy	Antitoxin in Thousand Units	Antibiotics	Relaxants and Sedatives	Outcome
GR	1	?	15	M	Cauc.	Student	7	No	Yes	40 to wound 103 systemically	80,300,000 u. Penicillin Chloramphenicol 7 gm. Erythromycin 6 gm. Neomycin 1 gm.	Amobarbital Na 5 gm. Phenobarbital Na 0.14 gm. Tribromoethanol (rectally) 15 ml. D-tubocurarine in bee's wax .004 gm.	Died
AB	2	?	24	F	Negro	Housewife	6	? TAT	No	10 to wound 500 IV	600,000 u. Penicillin	Paraldehyde (IM) 10 ml. Diphenhydramine HCl (IM) 100 mg. Phenobarbital Na 4 gr.	Died 6 hrs.
JRB	3	No	19	M	Cauc.	Laborer	?	For previous wounds	No	150 (Desensitized)	Streptomycin 1.0 gm. Chloramphenicol 5.0 gm.	Amobarbital Na 36 gm. Elix. Tolserol (Myanesin) 167 gm. Chlorpromazine 3.325 gm. Tripelennamine HCl 3.350 gm.	Recovered 26 days
AD	4	No	87	F	Cauc.	Housewife widow	10	No	No	12 to wound 710 systemic	116,000,000 u. Penicillin Erythromycin 1 gm. Chloramphenicol 9 gm. Oxytetracycline 1.1 gm	Elix. Tolserol (Myanesin) 154 ml. Phenobarbital Na 24 gr. Amobarbital Na 22.5 gr.	Died 6th day

RF	5	Yes	34	M	Cauc.	Farmer	? 30	No	Yes	640	14,200,000 u. Penicillin Chloramphenicol 11 gm.	Luminal Na 6 gr. Pentobarbital Na 33 gr. Amobarbital Na 1,110 gr.	Recovered 33 days
CS	6	No	15	M	Cauc.	Student	8	No	No	140	12,300,000 u. Penicillin	Luminal Na 70 gr. Amobarbital Na 115 gr. Ether in oil 2 ox. Seconal Na 3 gr.	Recovered 24 days
JCR	7	No	53	M	Negro	Laborer	8	No	No	80	92,400,000 u. Penicillin	Phenobarbital Na 5 gm. Chloral Hydrate 2 gm. Phenergan HCl 1.253 gm.	Recovered 24 days
MA	8	No	84	M	Cauc.	Retired	14		Yes	160	90,000,000 u. Penicillin Chloramphenicol 4 gm. Novobiocin 3 gm.	Amobarbital Na 12½ gr. Phenobarbital Na 12 gr. Chloral Hydrate 75 gr.	Recovered 28 days
MB	9	No	22	F	Cauc.	Teacher	8	No	No	25 to wound 230 systemic	Chloramphenicol 4.5 gm.	Phenobarbital Na 1.00 gm. Seconal Na 0.1 gm. Phenergan HC .0175 gm. Mephenesin 2.5 gm. Elix. Tolserol (Myanesin) 8.5 gm.	Recovered 11 days

hospital day and recovery thereafter was complete and uneventful.

CASE 7. The patient was a 53-year-old Negro laborer who had developed generalized tetanus and "lockjaw" 7 days after cutting his hand in a garbage dump where he worked. Therapy with intravenous Sodium Amytal, Phenergan, 70,000 units of gas gangrene antitoxin, and 10,000,000 units of penicillin resulted in control of the severe generalized seizures. Intensive sedation with Phenergan Hydrochloride and sodium phenobarbital was necessary for 10 days. At the end of that time, it was possible to decrease the amount of therapy and sedation was stopped at the end of the thirteenth day in spite of the fact that mild abdominal tetanus occurred, for another week. Tracheostomy was not performed because the patient's tremendous musculature made him almost unmanageable during the acute phase and it was deemed safer to forego the operation.

CASE 8. The patient was an 84-year-old white man who was admitted to Mt. Sinai Hospital one week after he had removed a splinter, which had been in his forearm 7 days. On admission, he had severe trismus and generalized tetanus. Saliva was oozing from the sides of his mouth and he was choking and cyanotic. He had the typical facial expression of "risus sardonicus." He was given intravenous Sodium Amytal and an emergency tracheostomy was performed. One hundred thousand units of antitoxin and 40,000,000 units of penicillin were given intravenously, and 40,000 units of antitoxin were injected around the raised, reddened puncture site on his left forearm. Twenty-five milligrams of Phenergan Hydrochloride, intravenously, permitted adequate control of tetanic seizures with just an additional 3.5 grains of Sodium Amytal during the next 24-hour period. A stomach tube was used to maintain nutrition. Hypostatic pneumonia developed on the fifth hospital day and this was treated successfully with novobiocin and chloramphenicol. Tetany became less severe within 24 hours, although moderate contractions occurred for one week, and mild abdominal and arm contractions continued during the second week. The tracheostomy tube was removed on the tenth hospital day and the patient was discharged 29 days after admission with no residual complaints.

CASE 9. The patient was a 22-year-old school teacher who stepped on a tack on her basement stairs. The tack penetrated her tennis shoe and broke the skin of her foot. Ten days later she developed pain in her neck. She was seen by a physician who, assuming the complaint was related to a wisdom tooth, referred her to a dentist. The next day she could not open her mouth far enough for the dental examination so the dentist suggested the use of hot packs on her jaw and told her to return 2 days later. On the following day, the patient became dyspneic, could barely open her mouth and noted stiffness "over the entire body." Her mother suggested that she might have "lockjaw" and called the physician who then admitted the patient to the hospital. When examined, she had a small red area on the sole of her foot and her jaw was in frank trismus. Therapy was instituted immediately and consisted of 75,000 units of antitoxin, intravenously; 25,000 units of antitoxin infiltrated into the wound; Phenergan Hydrochloride, 25 mg., and mephenesin (Mydnesin), 0.5 gm. orally; chloramphenicol, 2 gm. intravenously (patient was penicillin sensitive); and sodium phenobarbital, 3 gr. orally. Symptoms did not progress and, after 48 hours, gradual improvement began. Medication was gradually decreased in dosage and all therapy was stopped on the eighth hospital day. At discharge on the tenth hospital day, the patient had only slight residual soreness of the jaws.

Discussion. It must be emphasized that tetanus is a preventable disease. All of these cases of tetanus probably could have been prevented had the patients been actively immunized with tetanus toxoid. Standard immunization consists of three injections of either alum precipitated or fluid tetanus toxoid, administered at monthly intervals followed by "booster" injections one year later and at 4- to 5-year intervals or at the time of injury (Edsall[4]).

The fact that 2 of the young patients died in spite of having received penicillin, in what was thought to be relatively large doses, is also worthy of emphasis. Admittedly, the penicillin was not the long-acting repository form suggested recently by Filler and Ellerbeck[5] but was a preparation which many physicians, who have reservations about long-term hypersensitivity reactions due to benzathine penicillin G, might be tempted to use. This failure of penicillin to protect against tetanus

was first mentioned by Altemeier in 1946[1]. If, in addition to the penicillin, these 2 patients had been given 3,000 to 5,000 units of tetanus antitoxin immediately after injury, their fatal tetanus probably would have been prevented (Edsall[4]).

The incidence of penicillin reactions has increased steadily and a significant percentage of these are fatal. Welch and Marti-Ibañez[10] reviewed 2,517 penicillin reactions of which 901 were life threatening and 809 of the anaphylactoid type. A total of 72 deaths was recorded. Penicillin may be acquired by the general population in a variety of subtle ways, including milk, poliomyelitis and adenovirus vaccines, or possibly contaminated syringes (Nilsson and Sisson[8]).

On the other hand, Moynihan and Camb[6] reported an incidence of 5.8% reactions in 7,580 patients receiving tetanus antitoxin. About half of the reactions were minor, and about half or 192 were of the serum sickness type. There were only 2 cases of anaphylactoid reactions. The risks of hypersensitivity to horse serum and penicillin must be weighed in the prophylaxis of the tetanus prone wound.

The trivial nature of the wounds in several of the patients in this series tends to point out the danger of using too fine a clinical judgment in deciding who, among the nonimmunized patients, should receive antitoxin. In our opinion, patients, who exhibit hypersensitivity to horse serum on the preliminary skin test, should be given the bovine antitoxin rather than horse antitoxin in a desensitizing method. Penicillin may be used as an additional prophylactic measure but ordinarily should not be necessary if debridement and antiserum are used (Edsall[4]).

The diagnosis of tetanus usually is apparent and lockjaw or trismus is the most common presenting symptom. Tetanus of the muscles of the abdominal wall and back usually begins at about the same time. Risus sardonicus is indeed an apt description of the patient's facial expression. The disease almost never occurs in persons in whom active immunity has been maintained. The cornerstones of therapy are antitoxin, sedation, antibiotics and maintenance of a patent airway.

Retrospectively, probably too much antiserum was used in this group of patients, since 100,000 units given intravenously and 25,000 units injected locally should be adequate to neutralize circulating toxin in the course of this disease (Edsall[4]).

During the course of this series, less and less sedation was used until the last 3 patients were kept at a level of consciousness sufficient to prevent active tetanus. Phenergan given intravenously in 25 mg. doses appeared to potentiate Sodium Amytal and made it possible to keep the dosage below levels that tend to cause respiratory depression. Sodium Amytal and sodium phenobarbital seemed adequate for sedation and no marked advantage was demonstrated by the addition of mephenesin or Avertin. Intramuscular methylbromate was not available during the course of this series; its use, as suggested by Perlstein[9], might further decrease the necessity for large doses of barbiturates.

This series demonstrated the futility of dogma regarding tracheostomy. It can be simply stated that some patients needed tracheostomy and some did not. Our inclination was always to have a tracheostomy performed if there was any question that it might become necessary.

Penicillin is the antimicrobial drug of choice in the therapy of tetanus and was used in large doses in all nonsensitive patients. In only one patient was surgical debridement used, since

usually the wound did not lend itself to the procedure and was trivial. Therefore, the large doses of penicillin were used to penetrate inapparent, perhaps overlooked, foci of organisms. Other antibiotics were added when secondary infections of significant nature occurred. Nutrition was maintained by intravenous therapy until it was felt nasogastric tube or oral feeding could be safely tolerated.

Summary and Conclusions. Nine cases of tetanus seen in an urban community are presented. Probably all could have been prevented by active or passive immunization. Two fatal cases developed in spite of early injections of penicillin. Most of the patients were respectable citizens of good nutrition and habits. Adequate treatment of tetanus consists of at least 100,000 units of antitoxin, large doses of penicillin, minimum necessary sedation with barbiturates potentiated by antihistaminics and mephenesin (Mydnesin), tracheostomy if necessary, and meticulous nursing care in a quiet, darkened environment.

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SUMMARIO IN INTERLINGUA

Tetanos in un Communitate Urban

Es presentate 9 casos de tetanos vidite in un communitate urban. Il es probabile que omnes haberea essite prevenibile per immunisation active o passive. Duo casos mortal se disveloppava in despecto de precoce injectiones de penicillina. Le majoritate del patientes esseva respectate citatanos de bon nutrition e de habitudes salubre. Un adequate tractamento de tetanos consiste de al minus 100.000 unitates de antitoxina, grande doses de penicillina, e le minimo necessari de sedation con barbituratos potentiate per antihistaminicos e mephenesina (Mydnesin). Tracheostomia es a effectuar si necessari, e un meticulose assistentia infirmari debe esser providite in un ambiente quiete e obscurate.

PULMONARY ALVEOLAR PROTEINOSIS

A REPORT OF 2 CASES. THE DIAGNOSTIC VALUE OF PERCUTANEOUS NEEDLE LUNG BIOPSY

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Since Rosen, Castleman, and Liebow[22] described the histologic changes of pulmonary alveolar proteinosis and reported 27 cases, 28 additional cases have been collected in the world literature (Bianco and Tomatis[1], Burbank, Morrione and Cutler[2], Carabasi and Barta[3], Carlson and Mason[4], Edmondson and Brewester[5], Fraimow *et al.*[6], Fraimow, Cathcart and Taylor[7], Friedman and Strickland[8], Furst, Bell and Irons[9], Hall[10], Harrison, Divertie and Olsen[11], Jones[12], Landis, Rose and Sternlieb[13], Levinson *et al.*[14], Lull *et al.*[15], McDowell, Williams and Hinds[17], Moertel, Woolner and Bernatz[18], Payseur, Konwaler and Hyde[19], Plenk *et al.*[20], Veterans Administration-Armed Forces[21], Shoen, Reingold and Meister[23], Sieracki, Horn and Day[24], Snider, Wilner and Lewis[25], Taxay, Montgomery and Wildish[26], Williams[27]). Due to the limited number of patients diagnosed and reported thus far, the principal features of this disease, other than the histologic pattern, are not as yet adequately characterized. The etiology, pathogenesis, therapy, and prognosis of pulmonary alveolar proteinosis are still not known. All the cases reported to date have been diagnosed by open chest procedure or on postmortem examination, with one single exception. In this instance the diagnosis was suspected on the basis of special sputum studies (Carlson and Mason[4]). Any technique other than exploratory thoracotomy, which may lead to histologic diagnosis of this disease in any suspected case, should be brought to general attention. This report presents the clinical and pathologic features of 2 additional cases of pulmonary alveolar proteinosis and indicates that such diagnosis can be established by the use of percutaneous needle lung biopsy.

Case Reports. CASE 1. On June 20, 1960, this 47-year-old white man (S.G., A-6760), a paint sprayer, was admitted to this hospital for evaluation of exertional dyspnea, which had been progressive since January, 1960. His exercise tolerance had gradually decreased to a 2 block walking dyspnea. During the same period of time he had had chronic

cough productive of about 1/3 cup of whitish sputum and associated with postnasal drainage. A tight feeling across his anterior chest, not related to exertion, had occasionally been noticed over the past several months. The past history revealed that the patient had been hospitalized previously for drainage of paranasal sinuses in 1938. Frontal headaches had been recurring periodically since. In 1950, a routine chest film had been taken by the local Mobile Unit and some abnormalities detected, for which it was suggested that the patient see his local physician. Because of the absence of symptoms at that time he had failed to seek medical advice. The remainder of the history and the review of

TABLE 1.—RESULTS OF THE PULMONARY FUNCTION TESTS IN THE 2 CASES

						Art. Blood		
	VC %	*VC, timed* % *at 2"*	*RV/TLC* %	*Alv. N_2* *conc.%*	*D* *ml. CO/mm. Hg/min.*	*pH*	*O_2 Sat.%*	*pCO_2* *mm. Hg*
Case 1, S.G.	84	100	26	.4	15.0	7.40	75	37
Case 2, R.H.	100	100	33	1.9	16.7	7.40	97	42

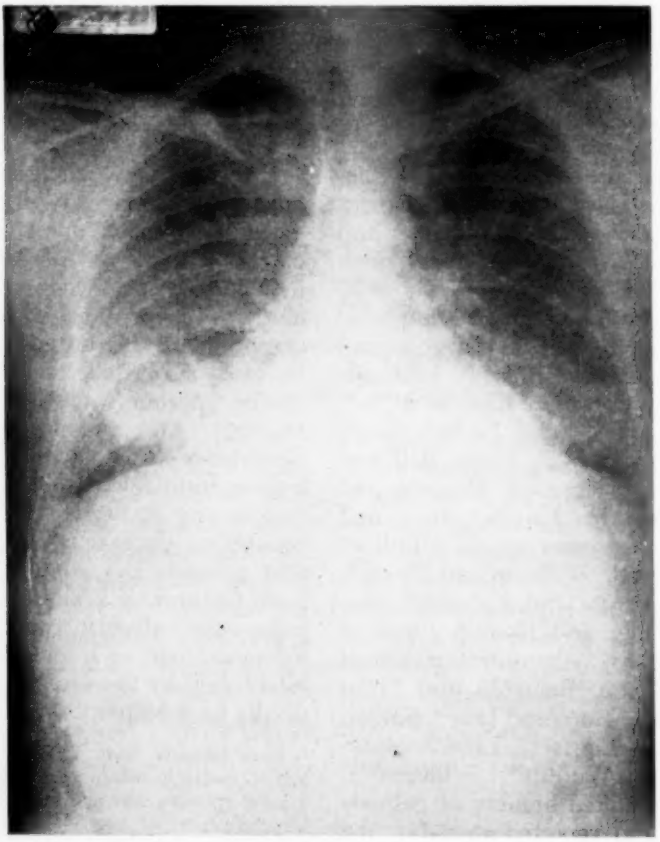

Fig. 1.—Case 1. Postero-anterior roentgenogram of the chest on July 19, 1960. Finely nodular densities scattered throughout the lung fields, more pronounced in the central and hilar regions.

systems were not contributory, with the exception of a weight loss of approximately 30 pounds during the present illness and a chronic exposure to some bronchial irritants because of the paint-spraying occupation.

On admission, he appeared well developed, well nourished, and in some respiratory distress. The blood pressure was 120/90 mm. Hg, pulse 90 per minute, and respiration 20 per minute. There was some tenderness to percussion over the frontal and maxillary sinuses. The chest appeared symmetrical and expanded well. There were moist inspiratory rales in the left base posteriorly and laterally. Minimal cyanosis was present, but there was no cardiovascular abnormality and no clubbing. The remainder of the physical findings was otherwise not remarkable.

Laboratory data were as follows: hemoglobin 17 gm. per 100 ml.; hematocrit 52 volumes %; white cell count 8,500 per c.mm. with normal differential. The urinalysis was unremarkable, so were the blood chemistry and liver function tests. The blood serologic test for syphilis was nonreactive. Electrocardiogram and electroencephalogram were within normal limits. The results of the pulmonary function studies are summarized in Table 1. Roentgenograms of the paranasal sinuses were negative. Roentgenograms of the chest revealed finely nodular densities scattered throughout both lung fields, more pro-

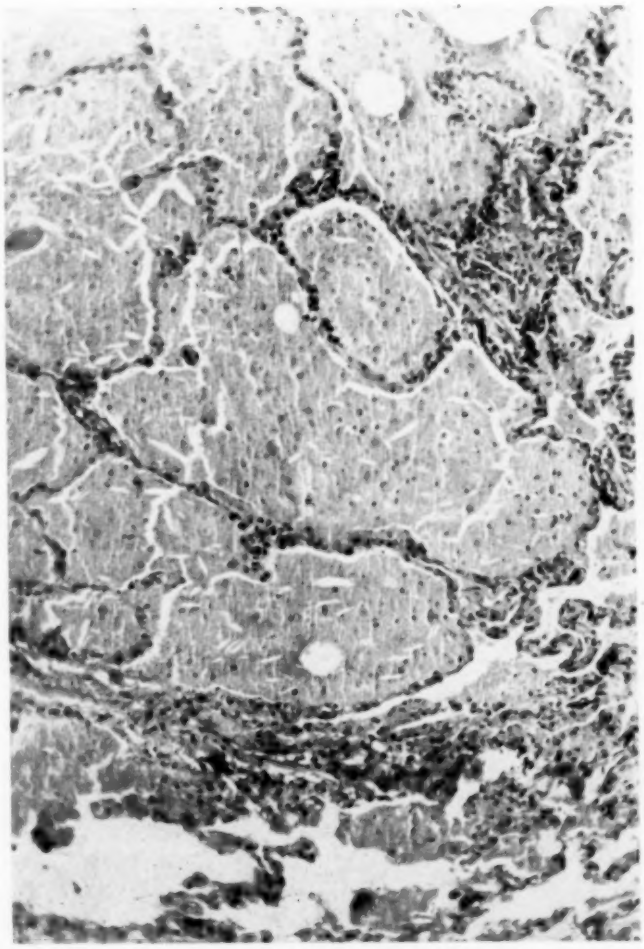

Fig. 2.—Case 1. Section of lung showing typical proteinaceous exudate in alveoli.

nounced in the central and hilar regions and fading peripherally into the bases and apices (Fig. 1). Skin tests for histoplasmin, blastomycin, coccidioidin, and tuberculin (PPD 1 and 2) were negative. Sputum smears and cultures on repeated occasions revealed no predominant organism, no mycobacteria, and no fungi.

On July 13, 1960, an open chest lung biopsy was obtained. An anterior thoracotomy was made on the right through the 4th intercostal space. The right lobe was not adherent to the parietal pleura and the fissures were distinct. The right lung had a reddish-brown appearance and was firm and indurated to palpation although crepitation was felt. No localized gross lesion was present, and since the entire right lung felt homogeneously indurated a small wedge excision was made of a portion of the right middle lobe.

This specimen consisted of a firm mass of tan and brown tissue measuring 2 × 1 × 0.5 cm. Cut surfaces were homogeneously tan and firm. Microscopic examination: the alveolar walls showed little change. Most of the alveolar spaces contained a somewhat granular, dull, eosinophilic material which filled them rather completely. Similar material was seen in some of the smaller bronchioles. This material contained a few scattered cells, some of which were lymphocytes and some

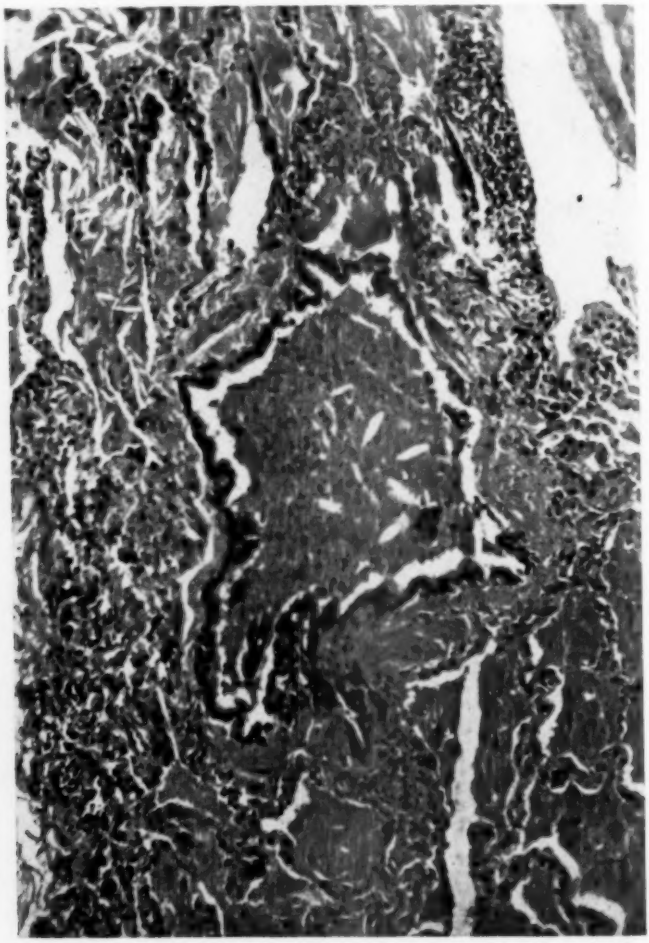

Fig. 3.—Case 1. Section showing typical exudate in bronchiole as well as alveoli.

of which appeared to be desquamated septal cells. Occasional rounded, markedly eosinophilic bodies without nuclei were also seen in the material. In many of the alveolar spaces the eosinophilic material was marked by considerable numbers of acicular spaces which appeared empty. Occasional alveoli contained large cells with foamy, vacuolated cytoplasm and small nuclei. In rare instances giant cells could be seen within alveoli. A moderate amount of anthracotic material was present. There were occasional small foci of lymphocytic infiltration. The alveolar walls appeared rather normal with the exception of undue prominence of septal cells. In periodic acid-Schiff stain preparation the exudate within the alveoli and the septal cells was strikingly positive. Small areas of atelectasis were seen in relation to the distended alveoli (Figs. 2–5). The pathologic diagnosis was pulmonary alveolar proteinosis. Cultures for fungi and acid-fast bacilli obtained from the operative specimen were unrevealing.

During the early part of the hospital stay the patient was treated with expectorants, bronchodilators, postural drainage, and broad spectrum antibiotics with noticeable decrease in cough and partial improvement in the degree of exertional dyspnea, although he still remained dyspneic on moderate exertion. Occasionally he complained of frontal headaches attributable to an allergic rhinitis and sinu-

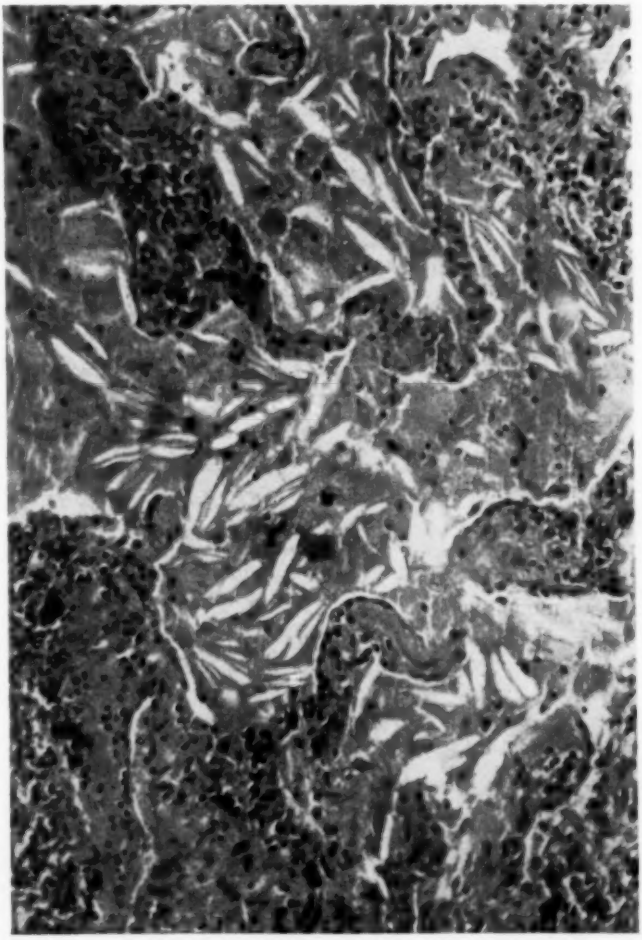

Fig. 4.—Case 1. Section showing typical acicular spaces and proteinaceous exudate.

sitis, which were controlled with symptomatic treatment. On November 23, 1960, he suddenly developed an increase in cough associated with temperature elevation, left-sided pleuritic pain, and blood streaked expectoration. During this episode he appeared somewhat dyspneic; his pulse rate increased to 110 to 120 per minute. Over the left midlung field a large area of dullness was elicited where vocal fremitus was depressed and breath sounds were replaced by inspiratory crepitant rales. No finding referable to venous disease could be elicited on careful examination of the lower extremities. Chest roentgenograms obtained at the onset of this acute episode demonstrated a triangular, rather homogeneous and large area of infiltration in the left mid-lung field anteriorly, compatible with pulmonary infarction for which the patient received appropriate treatment. Symptoms and signs of acute pulmonary infection persisted in spite of broad spectrum antibiotic therapy. Sputum smears and cultures revealed an overwhelming predominance of a streptomyces sp. Smears and cultures from a lung specimen obtained by direct needle aspiration through the chest wall confirmed the predominance of this organism in the involved area. The patient responded well to adequate sulfadiazine therapy.

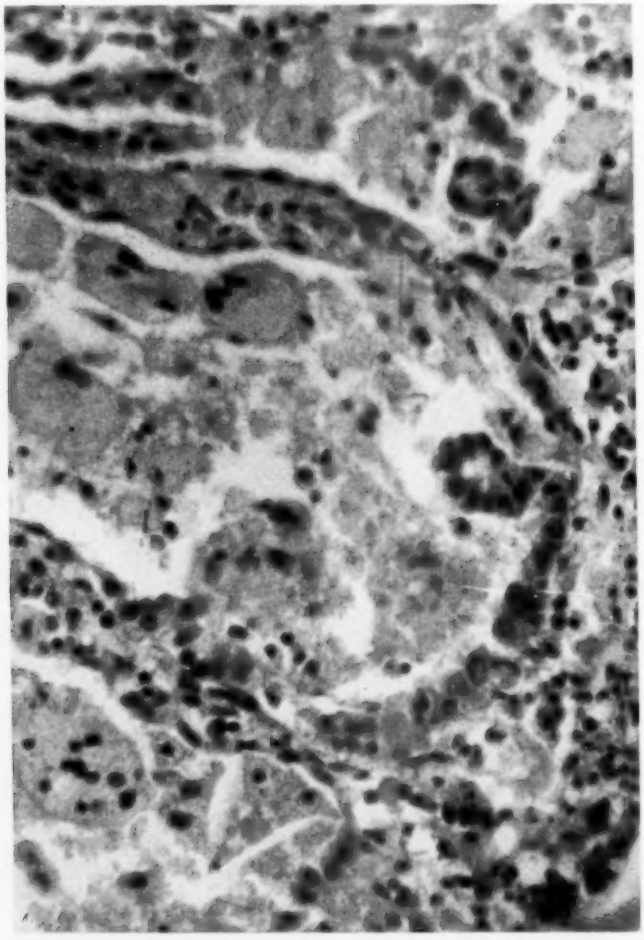

Fig. 5.—Case 1. High power view showing swelling and proliferation of septal cells and giant cells seen occasionally in the exudate.

CASE 2. A 41-year-old colored man (R.H., A-1311) was admitted to the surgical service on November 11, 1960, for treatment of hemorrhoids which had been symptomatic at intervals since 1946. The medical history revealed that at the age of 10 he had had a painless episode of "draining sinuses" on the right side of his neck, which cleared within 2 weeks and was thought to be blood serologic test for syphilis. Although he had been working regularly as a truck driver and more recently as a baker's helper up to the time of the present hospital admission, he had had no cardio-respiratory symptoms.

The physical examination upon admission to the surgical service was within normal limits except for a small scar on the right

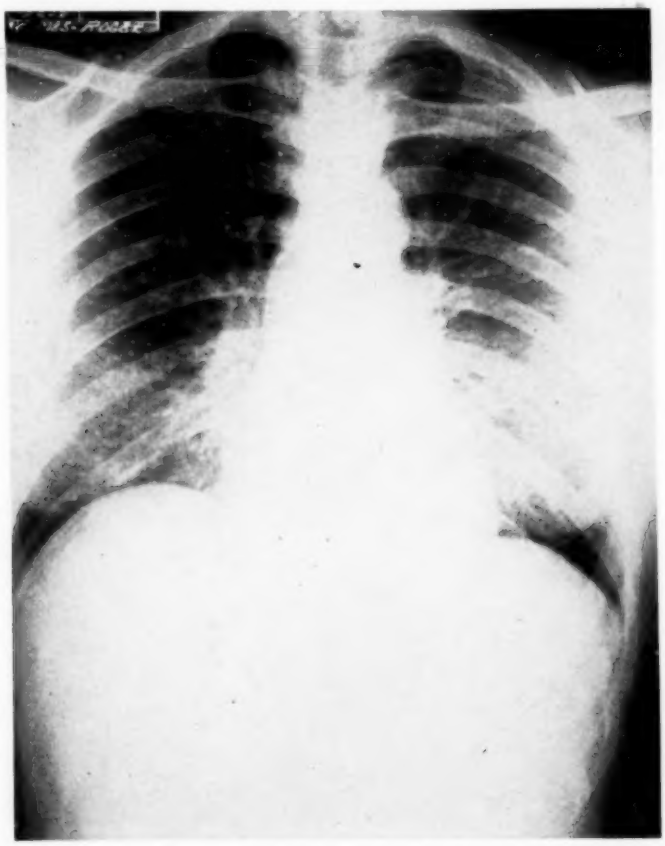

Fig. 6.—Case 2. Postero-anterior roentgenogram of the chest on April 1, 1959. No definite abnormality can be detected.

"scrofula." In April of 1959, he had been hospitalized for abscessed teeth and right lateral cervical abscess. Several teeth were removed at that time, and the abscess was treated by incision. The cultures from the draining material were found to be sterile. Other important laboratory findings during that hospitalization were a normal roentgenogram of the chest (Fig. 6) and a positive side of the neck and for the presence of an anal fissure with external hemorrhoids. Routine urine and blood analysis were unremarkable. A roentgenogram of the chest showed a diffuse, bilateral infiltrate which appeared to have progressed in comparison to a routine film taken on May 23, 1960. Both upper lobes contained mottled densities, more pronounced on the right than on the

left. The heart was of normal size and shape (Figs. 7 and 8). The patient was subsequently transferred to the medical service for diagnosis of the asymptomatic pulmonary disease. Again the physical findings, including slit lamp examination of the eyes, were not remarkable. Routine blood studies, cultures from gastric washings, liver function tests, and serum electrolytes repeated on several occasions were not revealing with the exception of the serum calcium, which ranged from 10.8 to 11.9 mg. per 100 ml. on 4 determinations with simultaneous serum phosphorus concentrations from 3.6 to 4.1 mg. per 100 ml. On a 150-mg. calcium diet the daily urinary calcium excretion was 214 mg. The blood serologic test for syphilis was weakly reactive. Histoplasmin and tuberculin (PPD 2) skin tests were negative. Pulmonary function tests are tabulated in Table 1. A liver biopsy showed no abnormality. Sputum smears and cultures for acid-fast bacilli and other bacteria were negative.

On November 21, a percutaneous needle lung biopsy was performed in an attempt to provide a definite diagnosis. A Vim Silverman needle was introduced under local anesthesia at the level of the 6th left intercostal space over the anterior axillary line in arrested end-expiratory position. The specimen obtained consisted of a slender, tan mass of lung tissue measuring 9 mm. in length and approximately 1 mm. in diameter. On microscopic examination, the alveolar walls in some places appeared thickened due to prominence of the septal cells. Some of these

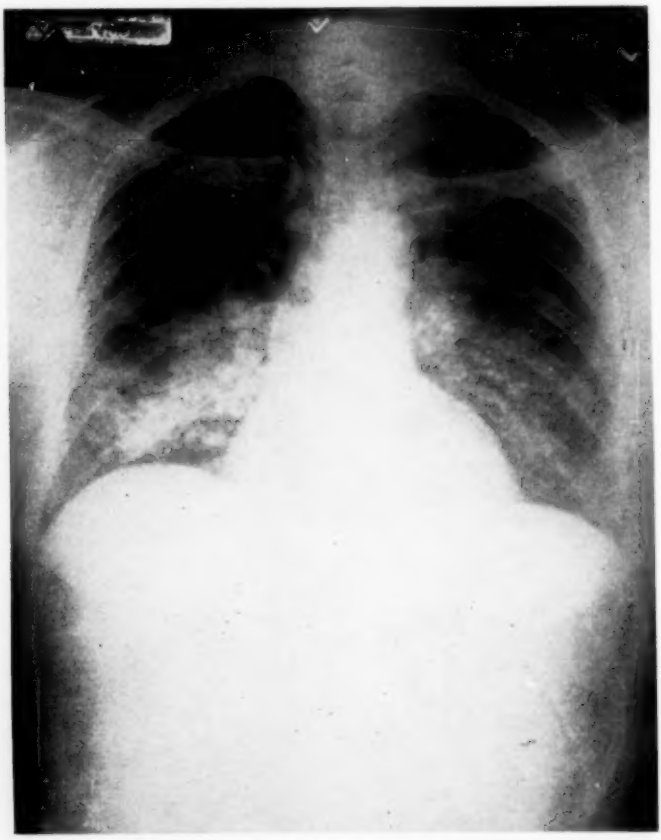

Fig. 7.—Case 2. Postero-anterior chest roentgenogram on May 23, 1960. Diffuse and irregular infiltrates in both lung fields.

appeared vacuolated, and a few of them appeared to be cast off into the alveolar spaces. Some alveolar spaces were filled with eosinophilic granular material in which there were occasional cleft-like spaces. Some clear vacuoles were also seen in this material. In addition, there were a few clear eosinophilic rounded bodies which appeared to be desquamated septal cells. The eosinophilic material generally was granular in appearance and much less uniform than edema fluid. No giant cell reaction was seen. The small vascular structures were not unusual in appearance. Sections stained by the periodic acid-Schiff method showed the eosinophilic material in the alveolar spaces to be markedly positive. Small amounts of PAS positive material were also seen in some of the septal cells. There was a moderate amount of anthracotic pigment, and no evidence of significant inflammation, neoplasm, or granuloma was seen (Figs. 9 and 10). The pathologic diagnosis was pulmonary alveolar proteinosis. Six weeks after admission the patient is still asymptomatic and repeat chest roentgenogram is unchanged.

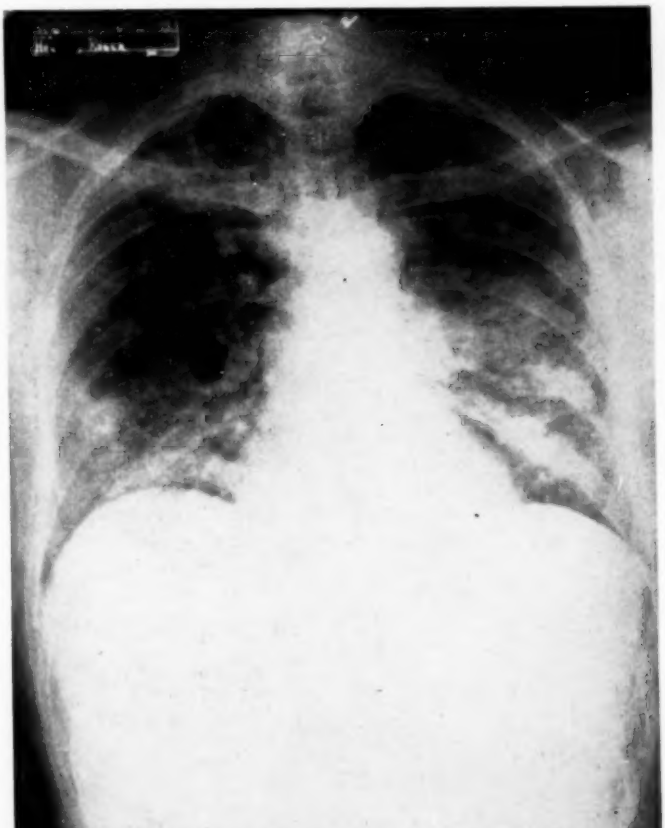

Fig. 8.—Case 2. Postero-anterior chest roentgenogram on November 11, 1960. There has been some extension of the infiltrates observed in the May 1960 film.

Discussion. The clinical course of these 2 patients with typical pulmonary changes of alveolar proteinosis is remarkably different. On the basis of a previous routine chest film allegedly abnormal, it could be speculated that the first patient had had pulmonary involvement for at least 10 years be-

fore he manifested respiratory symptoms. In January, 1960, dyspnea on exertion occurred and progressed rapidly. In the second patient there has been a rapid progression of the pulmonary involvement since May, 1960, as

Olsen[11], Payseur, Konwaler and Hyde[19], Rosen, Castleman and Liebow[22]).

As for the etiology of the disease, none of the suggested theories appears to be well supported. Our first patient during the hospital stay developed

Fig. 9.—Case 2. Entire needle biopsy specimen (× 40) showing typical lesion at lower end.

demonstrated by the serial roentgenograms, yet he is still asymptomatic. A marked variability of symptomatology of this condition has been reported by various authors (Fraimow *et al.*[6], Furst, Bell and Irons[9], Harrison, Divertie and

clinical symptoms and signs and radiologic findings strongly suggestive of an acute pulmonary vascular accident without evidence of peripheral venous disease. Subsequently, a large area of pneumonitis was discovered from

which a streptomyces sp. was cultured. Admittedly, the suspected pulmonary vascular accident could have been produced by embolization of asymptomatic venous thrombi formed in the lower extremities, in the pelvis, in the right side of the heart, or by local thrombosis within the pulmonary vessels. The streptomyces could have invaded the necrotic area in which a possible bacterial infection had been controlled by broad spectrum antibiotics. On the other hand, the fungal infection *per se* could be considered responsible for the pneumonitis, with or without intravascular extension of the infectious process and secondary pulmonary infarction. The role of bacterial and fungal infection in this disease, if any, is yet to be defined (Burbank, Morrione and Cutler[2], Jones[12], Rosen, Castleman and Liebow[22]).

Although pulmonary alveolar proteinosis has been reported in associa-

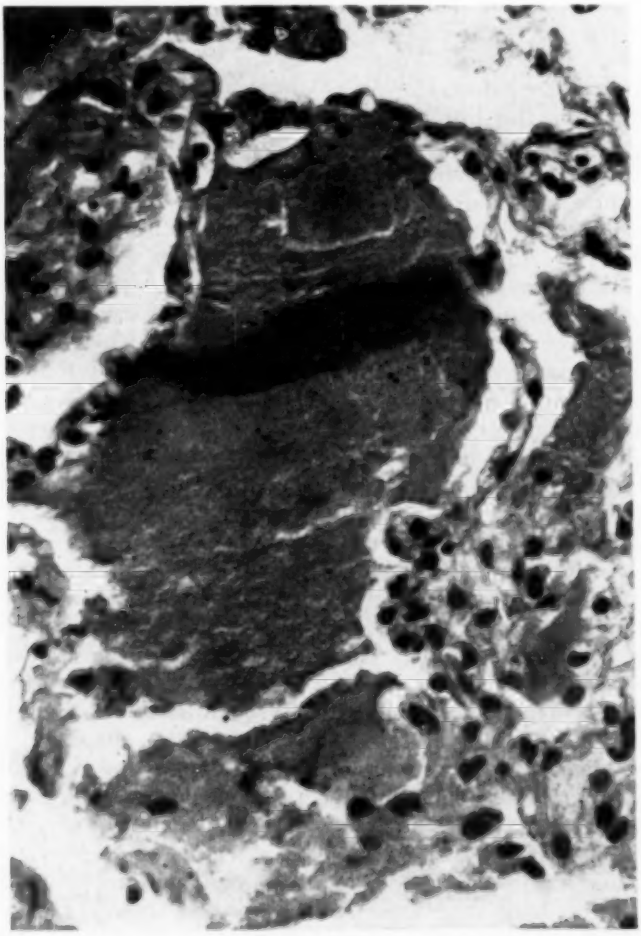

FIG. 10.—Case 2. High power view, showing PAS positive exudate in alveolus as well as septal cell hyperplasia.

tion with Weber-Christian disease (Shoen, Reingold and Meister[23]), with thrombotic thrombocytopenic purpura (Levinson *et al.*[14]), and with involvement of kidneys and peripheral veins (Landis, Rose and Sternlieb[13]), no common etiologic agent can at present be implicated in this disease. It may be postulated that pulmonary alveolar proteinosis represents a peculiar, yet uniform, type of reaction of the lung structures to different stimuli, whether chemical, physical, or infectious. It is interesting that both our patients, for occupational reasons, were exposed to chronic bronchial irritants, namely paint spraying and flour dust. However, any deduction from this history of exposure would be purely speculative.

Evidence of altered fat and protein metabolism in association with pulmonary alveolar proteinosis has also been presented (Landis, Rose and Sternlieb[13]). To our knowledge, hypercalcemia has not been described in this disease. In our second patient, this laboratory finding, in association with the clinical course of the disease, the radiologic picture, and the negative tuberculin skin test, had strongly suggested the diagnosis of sarcoidosis. Serum phosphorus and urinary calcium values in this patient were within normal limits. No radiologic sign of impaired bone metabolism was detectable, and the routine renal function studies indicated no evidence of kidney disease. The value of the isolated elevation of the serum calcium in this case remains to be assessed.

Since the clinical and laboratory findings of pulmonary alveolar proteinosis are so scanty, variable, and ill-defined, the diagnosis of this disease has to be based upon the histologic appearance of the lung structures. It has been pointed out that special sputum studies can be of diagnostic aid (Carlson and Mason[4]). On the basis of this suggestion, sputum samples were obtained from our patients and fixed with formalin. Sections were then prepared by usual histologic techniques and stained by the periodic acid-Schiff method. In both cases the microscopic appearance of the sputum resembled somewhat the changes originally reported by Rosen and associates[22] in the alveolar exudate. However, in neither case was the sputum diagnostic since mucin is PAS positive and alveolar casts were not found. Similar sputum characteristics were observed in other disease states, such as pulmonary tuberculosis, bronchogenic carcinoma, bronchiectasis, and lung abscess. The diagnostic value of these sputum findings, including PAS stains, requires further evaluation. For the present time, histologic examination of the lung parenchyma should be used to confirm the diagnosis.

It has been shown that percutaneous needle lung biopsy is a procedure virtually free of complications as long as it is performed in arrested end-expiratory position, and that it is of some value in diagnosing certain types of diffuse pulmonary diseases (Manfredi *et al.*[16]). As demonstrated in our second patient, a lung specimen suitable for histologic studies was obtained without difficulty by using this technique. The limitations of this procedure are obvious. Lung specimens may not be obtainable, may not be suitable for histologic examination, or finally may be taken from an uninvolved area of the lung, and in such instances the diagnosis will not be forthcoming. However, since percutaneous needle lung biopsy is reasonably safe and certainly of great simplicity, an attempt should be made to provide histologic material for studies with this technique. Open chest lung biopsy should be utilized as a diagnostic procedure only if a satisfactory diagnosis cannot be established by this method.

Summary. 1. Two patients with pul-

monary alveolar proteinosis are presented. The radiologic and histologic findings are similar in the 2 cases. The first patient had marked symptoms and signs of impaired pulmonary ventilation. During the hospital stay he developed an acute illness with a pulmonary fungal infection and possibly a pulmonary infarction. The second patient was asymptomatic and had no significant physical findings. A persistent hypercalcemia was observed in this second case. The clinical and laboratory aspects of the disease in these 2 patients are discussed.

2. The histologic documentation of the pulmonary lesion was provided by percutaneous needle lung biopsy in one of the patients and by exploratory thoracotomy in the other. In both patients sputum examination revealed the presence of proteinaceous material which was positive by periodic acid-Schiff stain. Since similar sputum findings were observed in other pulmonary disorders, no diagnostic value could be attached to this laboratory procedure.

3. A larger series of patients with pulmonary alveolar proteinosis needs to be accumulated before the nature and the course of the disease can be clarified. Simple diagnostic methods may be of great value in this clinical problem. It is suggested that whenever this condition is suspected, percutaneous needle lung biopsy be attempted to provide the necessary histologic diagnosis before an open chest diagnostic procedure is considered.

ADDENDUM: Since this paper has been written, an additional report has been presented by S. H. Rosen (U.S. Armed Forces Med. J., **11**, 1507, 1960). In this paper Rosen mentions 23 patients in addition to the 27 previously reported by him making a total of 50 cases which have been seen at the Armed Forces Institute of Pathology. It is very likely that many of these 23 additional cases have also been reported separately in the various papers referred to in our bibliography.

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SUMMARIO IN INTERLINGUA

Proteinosis Pulmono-Alveolar

1. Es presentate le casos de duo patientes con proteinosis pulmono-alveolar. Le constatationes radiologic e histologic in le duo es simile. Le prime patiente habeva marcate symptomas e signos de degradation del ventilation pulmonar. Durante le sojorno al hospital, ille disveloppava un maladia acute con infection fungal del pulmones e possibilemente un infarcimento pulmonar. Le secunde patiente esseva asymptomatic e habeva nulle significative alterationes physic. Un persistente hypercalciemia esseva observate in iste secunde caso. Le aspectos clinic e laboratorial del morbo in ambe patientes es discutite.

2. Le documentation histologic del lesion pulmonar esseva providite per un percutanee biopsia a agulia del pulmon in un del patientes e per thoracotomia exploratori in le altere. In ambe patientes le examine del sputo revelava le presentia de materiales proteinacee que esseva positive in tincturation con acido periodic Schiff. Viste que simile constatationes in le sputo esseva observate in altere disordines pulmonar, nulle valor diagnostic poteva esser attribuite a iste mesura laboratorial.

3. Un plus extense serie de patientes con proteinosis pulmono-alveolar debe esser accumulate ante que le natura e le curso del morbo pote esser clarificate. Simple methodos diagnostic esserea de grande valor in iste problema clinic. Es recommendate que—quandocunque le suspicion de iste condition existe—biopsia a agulia del pulmon es essayate pro obtener le datos necessari pro un diagnose histologic ante que on considera effectuar un exploration diagnostic a thorace aperte.

SEVERE INTERSTITIAL EMPHYSEMA, PNEUMOMEDIASTINUM, AND PNEUMOTHORAX: UNCOMMON COMPLICATIONS OF HYALINE MEMBRANE DISEASE*

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The sudden onset of respiratory distress with cyanosis in the newborn always carries a serious prognosis. One of the common causes is hyaline membrane disease. Another is spontaneous pneumothorax and pneumomediastinum. While pneumothorax and pneumomediastinum in the adult is considered a benign disease (Dencer[4], Hamman[12]), in the newborn it may be fatal, although the pathophysiology is probably the same in both age groups (Macklin[17], Norman and Rizzolo[18]). Hyaline membrane disease in the newborn has been well established (Gruenwald[11], Potter[21], Saphir[22]), as has pneumothorax and pneumomediastinum secondary to a variety of causes (De Costa[5], Ebner[6], Hurwitz and Greenhood[15], Smith and Bowser[23]), but the simultaneous occurrence of the two diseases to our knowledge has not been stressed in the literature. Severe interstitial emphysema in mature infants is usually secondary to energetic reanimation because of anoxia due to a variety of causes, and hypoplastic lungs. It is the purpose of this study to review the clinical and pathological findings in 2 full-term infants with hyaline membrane disease and interstitial emphysema with pneumomediastinum and pneumothorax, and to suggest a causal relationship of one to the other.

Case Reports. CASE 1: This was a full term white male infant of 40 weeks' gestation. The delivery was spontaneous and uncomplicated. The mother was 34 years old and gravida V, para IV. She was not diabetic. The infant's cry was spontaneous and no form of artificial resuscitation was used. He weighed 3,410 gm. at birth and measured 51 cm. from crown to heel. Four hours after birth grunting respirations and retractions of the chest were noted. The systolic blood pressure was 48 mm. Hg. No cyanosis was visible. The heart appeared normal and the lungs were clear to auscultation and percussion. The Moro reflex and cry were good. The child was placed in an oxygen tent with 40% humidity. At 30 hours of age the respirations had not improved but became more labored. Cyanosis now became apparent. Breath sounds were absent over the left side of the chest with hyperresonance to percussion. Roentgenograms revealed a tension pneumothorax (Fig. 1). The right side of the chest was not remarkable. No hepatosplenomegaly was noted. One hundred and seventy centimeters of air were aspirated from the left chest. The child did not respond; he remained cyanotic and expired 2 hours later at 32 hours of age.

The necropsy revealed a left pneumothorax with pneumomediastinum and focal subpleural emphysema of the lower lobe of the left lung. Grossly the lungs were moderately full, yet noncrepitant and purplish-red. The tracheobronchial tree showed no evidence of obstructive disease. Microscopically many alveolar spaces were collapsed. The septal

* This study was supported by a grant from the Wilmette Myocarditis Research Fund.

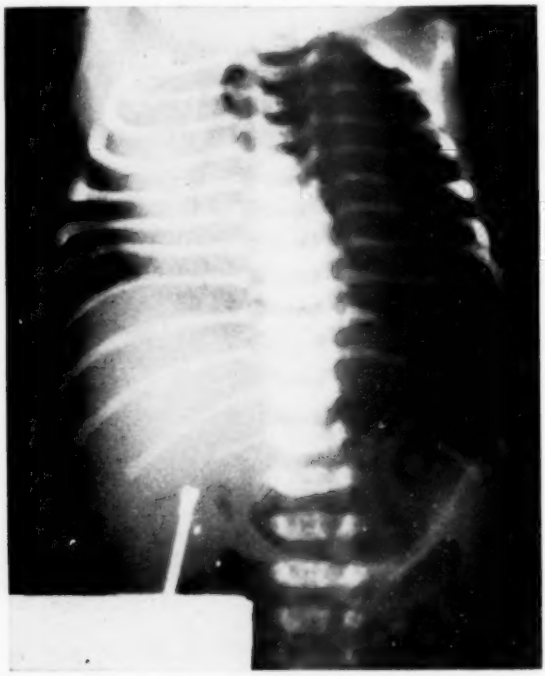

Fig. 1.—*Case 1:* Roentgenogram of chest (A.-P. view) showing left tension pneumothorax with considerable shift of heart and mediastinum to right side of thorax.

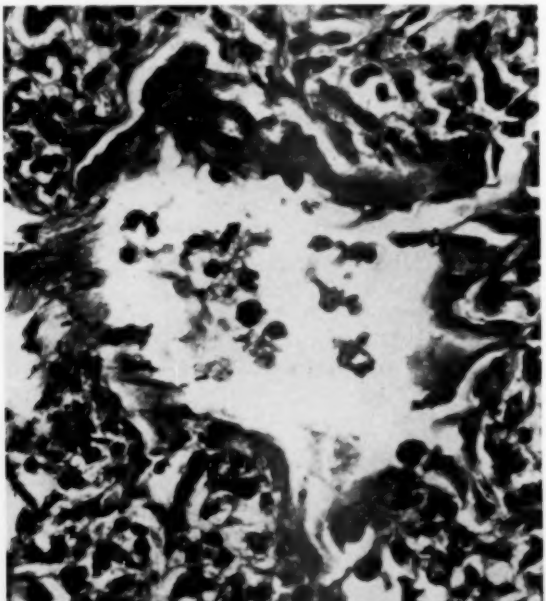

Fig. 2.—*Case 1:* Lung section showing typical hyaline membrane. (Hematoxylin and eosin preparation, ×375.)

capillaries were engorged with blood. Many other alveolar spaces and ducts were dilated and uniformly lined by irregular, deeply eosinophilic, fibrin-like membrane (Fig. 2). The morphologic features and tinctorial stains were characteristic of the so-called hyaline membrane. In the periadventitial tissue of the larger blood vessels were irregular empty spaces which did not appear to be related to lymphatic channels but obviously were spaces containing air (Fig. 3). These spaces were not found in the peribronchial fibrous tissue sheaths.

Fig. 3.—*Case 1:* Lung section showing perivascular air channels unrelated to lymphatic spaces. (Hematoxylin and eosin preparation, ×90.)

CASE 2. This white male infant was transferred from another hospital following delivery by Cesarean section. The mother was gravida III, para I. Her two previous deliveries were also by Cesarean section. The maternal type was O, Rh positive, and the serologic tests proved negative. The pregnancy was normal. The Cesarean section was uneventful. Under general anesthesia the interval between the start of anesthesia and the birth was 10 minutes. The infant's cry was spontaneous. His birth weight was 3,163 gm. and his crown to heel length was 49.5 cm. The child was transferred to the nursery in fairly good condition. Six hours later the child was in respiratory distress with cyanosis. Therapy consisted of oxygen and intramuscular injections of penicillin and chymotrypsin in sesame oil and Lobulin. Roentgenographic examination suggested the presence of a pneumomediastinum. A right thoracentesis failed to obtain any air or fluid. The pulse was 120 per min. Subcostal retractions were noted. No dullness was present and breath sounds were heard over both lungs. The heart was not remarkable. Hepatomegaly was present. The muscle tone and Moro reflex were now poor.

Upon admission to our institution at 47 hours of age, the child was in severe respiratory distress with a moaning cry with each respiratory effort. He was cyanotic out of an oxygen tent. There was marked subcostal retraction. There was no dullness to percussion. Breath sounds were heard fairly well, although they were diminished over the left side. Fine, moist rales were present over both

lung fields. The heart tones were muffled at a rate of 120 per min. A chest roentgenogram on admission showed marked cardiomegaly with marked under-aeration of the right lung and poor aeration of the left lung. There was an air shadow in front of the cardiac border interpreted as representing either a pneumothorax, pneumomediastinum or pulmonary cyst (Fig. 4).

Fig. 4.—*Case 2:* Roentgenogram of chest (A.-P. view) showing pneumomediastinum.

A thoracentesis of the right chest yielded 50 ml. of air evidencing a pneumothorax and the infant seemed to improve momentarily. The respirations slowed to 50 per min. A few minutes later the respiratory rate increased and cyanosis again became apparent. A chest tube was inserted into the right pleural cavity. The child was digitalized with Cedilanid. The electrocardiogram showed a definitely abnormal curve with nonspecific changes. The infant expired at 52 hours of age.

At necropsy, multiple large subpleural air-containing blebs were present in the mediastinum. These did not extend above the lower border of the thymus. The lungs were firm and reddish-purple. No obstructive tracheobronchial disease was found. Microscopically the alveoli were lined with a pink, eosinophilic membrane-like material, which was characteristic of the so-called hyaline membrane. The septal capillaries were engorged with blood. In many areas the septal walls were apposed as slit-like spaces but others appeared overdistended. In the periadvential fibrous tissue of the large blood vessels were irregular empty spaces which did not appear to be related to lymphatic channels but were apparently filled with air, similar to those seen in the first case (see Fig. 3). Such spaces were not found in the peribronchial fibrous tissue sheaths.

Discussion. In both of these cases there was little or no change in the course of the disease, even though attempts were made to relieve the pneumothorax and pneumomediastinum. In both cases, in addition to the pneumothorax and pneumomediastinum, there

was pulmonary hyaline membrane disease.

No method of artificial resuscitation was used in either infant. In the first case a tension pneumothorax was recognized by Roentgen-ray and clinical findings. Potter[21] stated that, "It is questionable whether it (referring to tension pneumothorax) ever occurs in the newborn, except as a result of artificial resuscitation." Emery[7] reported a series of 100 newborns in which 52 were mature or postmature and 48 were premature. In the mature or postmature group, 14 infants had interstitial emphysema and pneumothorax with no history of artificial resuscitation. They expired between 4 and 49 hours of age. Thus, it appears that a spontaneous pneumothorax may occur in infants, and that there is no need to suggest mechanical mechanisms as the cause except possibly in the premature group. None of the 48 prematures died of spontaneous pneumothorax, although several had small amounts of interstitial emphysema produced by artificial respiration.

Upon gross examination of the lungs in our cases, no pleural tear or outspoken ruptured emphysematous bleb could be found. On microscopical examination a minute pleural tear was found in the left lung in Case 1 on the side corresponding to the pneumothorax. This may have been due to a needle puncture at the time of the aspiration of the pneumothorax or may represent the site of a minute ruptured emphysematous bleb. The rupture of such an emphysematous bleb may account for the pneumothorax but some other cause must be sought to explain the interstitial emphysema and pneumomediastinum (Fisher and Macklin[9], Glaser and Landau[10]). Emery[7] was able to show in 14 cases of interstitial emphysema and pneumomediastinum, that aspirated squamous cells mixed with amniotic fluid were blocking the smaller respiratory passages which he thought created an "air block" with the hyperdistension of the air spaces. This resulted in alveolar wall tears that allowed the dissection of air into the interstitium of the lungs. In our cases we were unable to identify a site of obstruction in the smaller respiratory passages, but hyperinflated alveoli and alveolar ducts were present and lined by a "hyaline membrane." Such overdistended alveoli, whatever their cause, are always a part of the histological pattern described with interstitial emphysema (Patterson and Fawcett[19]). Just as squamous cells mixed with amniotic fluid may act as a one-way air block, so it seems that the hyaline membrane may on occasion completely obstruct the alveolar ducts and, together with increased forceful respirations of the infants due to hypoxia, cause alveolar wall tears in areas of lungs which are hyperinflated with resultant interstitial emphysema and pneumomediastinum. Characteristically present were distended spaces in the sheaths of the pulmonic vessels where air dissected. These spaces were not present in the bronchial sheaths.

Macklin[17] was able to show that air, after it had broken from the pulmonic alveoli into the interstitial tissue of the lung, could travel along the sheaths of the pulmonary blood vessels in artificial channels which it dissects to the root of the lung and from there into the mediastinum. Such channels were not found in the bronchial sheaths or about the bronchial arteries (Glaser and Landau[10]).

The sequence of events is first that of an interstitial emphysema which dissects along the pulmonary vessels resulting in a pneumomediastinum. The resultant pneumothorax, when it occurs, is usually caused by a break through of the air at the hilum of the

lung into the pleural cavity (Hamman[12]). While "blow outs" of air can occur through the visceral pleura and cause pneumothorax (Glaser and Landau[10]), they appear to be quite rare. For some as yet unknown reason, the visceral pleura of the lung is particularly resistant to pressures of this type (DeCosta[5], Macklin[17]).

In the newborn infant with a pneumothorax or pneumomediastinum the severity of the disease may be partly due to the failure of the trapped air to break through into the subcutaneous or retroperitoneal spaces (Heald and Wilder[13]). This break-through or dissection in the fascial planes and subcutaneous tissue in the adult offers a release of pressure on the mediastinal structures, and may account for the benignity of the disease (Hurwitz and Greenhood[15]). In both of our cases there was no subcutaneous or retroperitoneal emphysema.

Another cause of the severity of pneumothorax in the infant is the effect of mediastinal shift. In the adult who has had multiple mild respiratory diseases or pleuritis, the mediastinal structures may be relatively fixed by fibrous adhesions, so that a pneumothorax is less likely to produce a mediastinal shift and a greater pressure may be required to produce a shift of the mediastinal structures than in the infant. In the infant who has not been exposed to such infections and fibrous healing, a mediastinal shift and compression atelectasis may occur easily with interstitial emphysema and pneumothorax due to the relative lack of fixation of the mediastinal structures.

Pneumomediastinum, if the air remains under pressure, may cause an "air vise" (Abramson, Rook and Nau[1], Fisher and Macklin[9]) with compression of the hilar pulmonary vessels. This causes pulmonary hyperemia, pulmonary edema, anoxia, and death, or death by cardiac decompensation. Certainly, at least two other forces are acting with pneumatization of the interstitial lung tissue. One is the interference with respiratory movements by the splinting action of air in the interstitial tissues of the lung (Abramson, Rook and Nau[1]). The second, creating anoxia, or at least hypoxia, is aberrant air distending the sheaths of the pulmonary blood vessels as it travels from the region of leakage, thereby narrowing or collapsing the vessels so that the blood flow is impeded or actually stopped (Fisher and Macklin[9]).

It is certain that the production of interstitial emphysema requires at least a partial obstruction of a portion of the respiratory tree and some increased respiratory effort. The latter may be the first lusty cry at delivery, or the forced respirations of the infant during respiratory distress. The obstruction may be represented by the insidious increase of hyaline membrane material in the alveolar walls or by aspirated material. It may be the use of a tracheal catheter with resuscitation. Once air has passed the ruptured alveolar wall and entered into the interstitium, the potential is established for a pneumomediastinum. At what pressure this rupture occurs at the alveolar level is not certain. Various pressures are recorded in the literature, and it is claimed that as little as 18 to 20 mm. Hg pressure could produce bullous emphysema in dogs (DeCosta[5]). Wilson[25] was able to produce alveolar wall tears in cats in the Drinker respirator at a negative pressure of 10 cm. of water. The exact pressure which will cause an alveolar tear in infants is unknown. Ebner[6] notes that on the first respiration the pressure within the thorax of the infant falls to a negative pressure of 60 to 80 cm. of water. With such low pressure in the experimental

animal and the high negative pressure known to occur with the first inspiration, it seems plausible that any severe respiratory effort may cause pneumatization of the vascular sheaths (Ebner[6], Emery[7]), interstitial emphysema, and result in a fatal disease of the newborn.

For the clinician, the chest roentgenogram aids in the diagnosis of the pneumothorax or pneumomediastinum. The diagnosis of hyaline membrane disease may be made by the radiologist by it "characteristic" reticulogranular appearance distributed throughout both lung fields in a homogeneous pattern (Feinberg and Goldberg[8]). Roentgenograms of the newborn lungs are technically difficult, and in the acutely ill child there may be a tendency to rush the diagnostic procedure to find a "treatable" disease. So it is possible to understand how one or the other of the characteristic signs may be obscured. A request not only for an anteroposterior view but a lateral view of the chest may aid in the diagnosis and will enable the radiologist to estimate the severity of the diseases and aid in the prognosis of the patient. The physical examination of the infant with pneumothorax will reveal hyperresonance of the side involved with decreased breath sounds, cyanosis, bulging intercostal spaces, and a shift of the mediastinum. There will usually be a tachycardia, tachypnea and grunting respirations. Hepatoptosis may be found. These signs may lead to the diagnosis of pneumothorax.

In attempting to classify the causes of pneumothorax and pneumomediastinum in the newborn infant, Hurwitz and Greenhood[15] gave the following classification:

1. Diseases of the lung (pneumonia with abscess formation).
2. Congenital defects (bronchopleural fistula, cysts and pulmonary vessel anomalies).
3. Traumatic injuries (direct fracture of ribs or clavicle, perforating wounds of the larynx, trachea, or bronchus, wounds of the neck or diaphragm).
4. Mechanical obstruction:
   a. External (enlarged thymus or thyroid, cord around the neck).
   b. Internal (mucus or vernix in the air passages).
5. Idiopathic or unknown.

DeCosta[5] offers a similar classification. He also divides pneumothoraces into those which develop suddenly and gradually as abruptio and lenta.

The problem becomes more complex when one attempts to place hyaline membrane disease in the classification for the exact nature of the hyaline membrane is still undetermined (Buckingham and Sommers[2], Gruenwald[11], Potter[21], van Breemen, Neustein and Bruns[24]). At least from our findings it appears that one of the underlying diseases aiding in the production of pneumomediastinum and pneumothorax is hyaline membrane disease.

Peterson and Pendleton[20], in contrasting the roentgenographic pulmonary patterns of hyaline membrane disease and fetal aspiration syndromes, found 5 cases among 104 with pneumothorax and pneumomediastinum. This series indicated that 5% of infants with pulmonary disease (reticulogranular pattern suggesting hyaline membrane disease by roentgenogram) may have had a pneumothorax or a pneumomediastinum, or both. One of their cases, having a reticulogranular pattern to the lungs, showed interstitial emphysema which was confirmed by necropsy. No remark of the presence or absence of a hyaline membrane at necropsy was made in reference to this case.

Air in the pleural cavities and mediastinum in the newborn may be asymptomatic. Davis and Stevens[3] reported

radiographic evidence of pneumothorax in 6 of 702 consecutive normal babies. Holt and McIntosh[14] reported 10% of newborn infants had small collections of air in the mediastinum. There is some variance in the reports in the literature as Keefe and Jones[16] found no pneumothorax or pneumomediastinum among 4,000 cases. It seems that air may be present in the pleural cavity in the newborn more often than suspected, but that the quantity is usually small and well confined and the child remains asymptomatic. These cases may well be the result of a rupture of an emphysematous bleb or pulmonary cyst which may produce pneumothorax but not interstitial emphysema or pneumomediastinum (Dencer[4]). Our cases illustrate the result of interstitial emphysema, pneumomediastinum and pneumothorax.

A small or early pneumothorax in the infant with the respiratory distress syndrome or the pulmonary syndrome of the newborn may, therefore, indicate a serious to fatal prognosis. It is not a benign disease and may be fatal in 13% of the cases (Emery[7]). It should lead to an investigation of the underlying pathology of the lungs which may aid in rational therapy and may explain why the aspiration of the pneumothorax or relief of the pneumomediastinum does not produce the expected dramatic relief of the cyanosis of the infant. It should be noted that in the newborn it is not likely to be a simple process of a "ruptured bleb" and that air in the pleural cavity may be the result of another underlying disease. In our 2 cases hyaline membrane disease was the underlying disorder. It is of interest that the hyaline membrane disease occurred in full term infants, one born spontaneously.

Summary. Two mature infants with respiratory distress syndromes are reported. Each had both hyaline membrane disease and interstitial emphysema with pneumomediastinum and pneumothorax. Each demonstrated "vascular air sheaths" on microscopic examination of the lungs. The roentgenograms in each case were diagnostic of pneumothorax and pneumomediastinum but failed to reveal evidence of the underlying hyaline membrane disease. These cases exemplify the multiple problems ever present in the respiratory distress syndrome of the newborn.

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SUMMARIO IN INTERLINGUA

Sever Emphysema Interstitial, Pneumomediastino, e Pneumothorace—Complicationes Infrequente de Morbo de Membrana Hyalin

Es reportate le casos de duo infantes nascite a termino con syndrome de angustia respiratori. Ambes habeva si ben morbo de membrana hyalin como etiam emphysema con pneumomediastino e pneumothorace. Ambes monstrava "vainas vascular de aere" del pulmones in le examine microscopic. Le roentgenogrammas in ambe casos esseva pathognomonic pro pneumothorace e pneumomediastino sed non revelava ulle evidentia de un subjacente latente morbo de membrana hyalin. Iste casos exemplifica le multiple problemas que es semper presente in le syndrome de angustia respiratori del neonato.

SPHEROID BODIES IN PLASMA CELLS*

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The presence of spheroid bodies in the cytoplasm of plasma cells has been the subject of many articles in recent medical literature. In 1955, Stich, Swiller and Morrison[7] described a plasma cell containing many opaque, blue, spheroid bodies. Since the appearance resembled a cluster of grapes, they introduced the term "grape cell." While the presence of "grape cells" in the bone marrow was considered by Stick, Swiller and Morrison to be diagnostic of multiple myeloma, Zlotnick[9,10] also observed these cells in cases of carcinoma of thyroid, acne conglobata, hepatic cirrhosis, arthritis and Waldenström's macroglobulinemia. In view of the wide variety of diseases in which "grape cells" were described, 22 of our cases of multiple myeloma were reviewed. Four additional cases showing "grape cells" are presented, one with myeloma and three with other diseases:

Case Reports. CASE 1. A 35-year-old steel worker was first seen by Dr. Leandro M. Tocantins on July 18, 1959, because of absence of sweating for a period of 4 to 5 years. The patient stated that on many occasions his skin would "burn," his face would become red, and at times he would become exhausted with concomitant difficulty in breathing. He denied other cardiac or respiratory symptoms.

Past medical history revealed he had two lymph nodes, which were normal, removed from his inguinal region the previous year. Seven to 8 weeks prior to our seeing him, the patient had been given liver and iron tablets after a bone marrow examination was performed, the results of which were not known.

Physical examination was within normal limits except for a slight pallor of the mucous membranes, shotty lymphadenopathy in the left axilla and both groins, and excoriations of the skin of both legs. The liver and spleen were not enlarged. The white blood cell count, platelet count, reticulocyte count, osmotic fragility of the red blood cells, hematocrit, and red blood cell count were within normal limits. The red blood cells appeared slightly hypochromic on examination of a peripheral blood smear. An unsaturated iron binding capacity was 230 μg. with a serum iron of 40 μg. per 100 ml. Hemoglobin electrophoresis with alkaline denaturation revealed the presence of hemoglobin A with 2.4% fetal hemoglobin. Serum electrophoresis disclosed 3.38 gm.% of albumin, 0.27 gm.% a_1 globulin, 0.60 gm.% a_2 globulin, 0.65 gm.% B globulin and 3.79 gm.% of G globulin. Roentgenograms of the skull, thorax, right thigh, sternum and pelvis showed no bony lesions.

A sedimentation rate was 6.5 mm. per hr. Urinalysis for Bence Jones protein was negative. Analytic ultracentrifugation was notable for the finding of an abnormal component with a sedimentation coefficient of 8.5 S (Svedberg Units). This component represented approximately 14% of the total protein. The 6.6 S component, which is usually com-

*The opinions or assertions contained herein are those of the authors and are not to be construed as reflecting the views of the Navy Department or the Naval Service at large.

posed largely, if not entirely, of gamma globulin was increased to 30% of normal. Combined, the 6.6 S and 8.5 S components represented 44% of the total protein and would account for the protein seen in the large gamma globulin peak on electrophoresis. A bone marrow demonstrated the presence of "Mott cells" and "grape cells" (Fig. 1). Also, a clump of immature plasma cells was found and considered to be myeloma cells.

mal component of 8.5 S found on ultracentrifugation. Sedimentation rates below 20 mm. per hr. were found by Snapper, Turner and Moscovitz[6], in only 10 of 97 cases of multiple myeloma. None of these had gamma globulins over 3.0 gm.%. The 8.5 S component occurs in multiple myeloma but

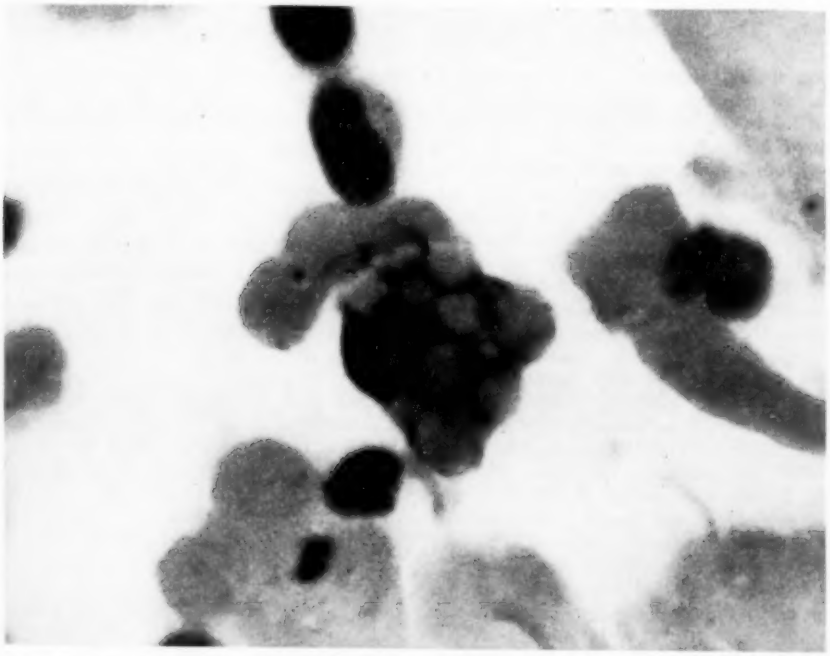

Fig. 1.—Shows "grape cell" with nucleus surrounded on one side by dark spheroid bodies. (×950)

COMMENT. Both "grape cells" and "Mott cells" were seen in this case. The "grape cells" contained blue spheroids which were intracytoplasmic while the latter contained clear spheroids, also intracytoplasmic. Because of the presence of myeloma cells, increased abnormal globulin, "Mott cells" and "grape cells," the diagnosis of multiple myeloma was considered. The unusual features of this case were the prolonged clinical course, the normal sedimentation rate and the abnormal is uncommon. Whether the ultracentrifuge findings, the sedimentation rate, the "grape cells" and "Mott cells" correlate is not known at the present time.

CASE 2. A 73-year-old, white woman was admitted to the U.S. Naval Hospital, Philadelphia, on November 16, 1958, because of progressive intermittent diarrhea of approximately one year's duration. Kaopectate and paregoric were given with partial relief. She noted that her stools were usually watery and brown, and, on a few occasions, black and watery.

Physical examination on admission was

within normal limits except for an oral temperature of 99.2° F., a regular pulse rate of 112, hepatomegaly 5 cm. below the right costal margin and splenomegaly 5 cm. below the left costal margin.

Laboratory studies on admission revealed a white blood cell count of 6700 per c.mm. with a differential of 47% neutrophils, 51% lymphocytes and 2% eosinophils. The patient's hemoglobin was 7.72 gm. per 100 ml. with a 26% hematocrit. A urinalysis showed a trace of albumin, but no abnormal cellular elements. VDRL, fasting blood sugar and a blood urea nitrogen were normal. Liver function studies disclosed a BSP retention of 12% in 45 minutes, cephalin flocculation of 3+ in 24 hours and 4+ in 48 hours, total protein 6.1 gm.% with 2.0 gm.% albumin and 4.1 gm.% globulin, prothrombin activity 92%, total cholesterol 145 mg. per 100 ml. and an alkaline phosphatase 7.25 Bodansky units. Blood studies, a few weeks later, revealed a leukocyte count of 1900 per c.mm. with 14% neutrophils, 84% lymphocytes, 2% eosinophils and a platelet count of 194,000 per c.mm. Urinalyses for Bence Jones proteins were repeatedly negative. Gastric analysis showed 8 units of free HCl. Serum electrophoresis revealed albumin 1.49 gm%, a_1 globulin 0.16 gm.%, a_2 globulin 0.29 gm.%, B globulin 0.31 gm.% and G globulin 3.84 gm.%. Corrected sedimentation rate was 33 mm. per hr. Roentgenograms of the chest, intravenous pyelogram and upper gastrointestinal series were within normal limits and a barium enema demonstrated evidence of diverticula. Bone survey revealed increased diploic content and a fine granular appearance of the calvarium, compatible with multiple myeloma. Liver biopsy microscopically exhibited diffuse fatty degeneration. Electrocardiograms were normal early in her hospital course, but later myocardial ischemia and digitalis effect were noted. A bone marrow examination performed on November 14, 1958, showed hyperplasia of all cellular elements with the presence of "grape cells." No "Mott cells" were noted in this case. The blue spheroid bodies of the "grape cells" were negative when stained with PAS. A Sia water test done on the serum was negative for macroglobulins.

Course. This chronically ill patient had intermittent fever, diarrhea, and skin abscesses in the inguinal area. She also experienced two episodes of pneumonitis, and deteriorated rather rapidly necessitating postponement of contemplated surgery for hypersplenism. However, with marked improvement after treatment of congestive heart failure, surgery was performed with removal of a 904 gm. spleen which revealed many areas of infarction and marked reticuloendothelial hyperplasia. Approximately one week later she became lethargic and unresponsive, and following this, progressively deteriorated and expired on January 26, 1959.

Necropsy. The findings of importance were limited to the abdomen. The liver was normal in size and shape, weighing 1350 gm. Microscopic sections showed considerable fatty metamorphosis and limited portal fibrosis with some areas of extravasation of red blood cells into the hepatic parenchyma. A section through the portal vein revealed an organizing thrombus with proliferation of fibroblasts and capillaries around the periphery of the thrombus.

COMMENT. This patient had "grape cells" in her marrow associated with hyperglobulinemic state secondary to limited portal cirrhosis. An unusual associated feature was the portal vein thrombosis with secondary hypersplenism.

CASE 3. A 48-year-old Negro male veteran was admitted to the U.S. Naval Hospital, Philadelphia on January 5, 1959, for evaluation of migratory polyarthritis. Two weeks prior to admission he had an upper respiratory infection with mild headache, neuralgia, sore throat and moderate nonproductive cough followed 2 weeks later by the appearance of persistent migratory polyarthritis involving both ankles, knees, shoulders, and elbows.

Physical examination on admission revealed a temperature of 100° F., pulse rate of 92 and a blood pressure of 142/88. The patient had tender swelling of the left knee and elbow joints and pain in all ranges of motion. The remainder of the physical examination was within normal limits.

Complete blood count, urinalysis, VDRL serology, fasting blood sugar and blood urea nitrogen were normal. Electrocardiograms were within normal limits except for a sinus tachycardia of 120 early in his illness. Roentgenograms of the sinuses, hands, shoulder girdles, lumbar spine, pelvis and chest were normal except for evidence of old, healed rib fractures bilaterally. Platelet counts, prothrombin time, coagulation time, bleeding time, sickle cell preparations, hemoglobin analysis, direct Coomb's test, Sia water test, and tests for cryoglobulins were within normal limits. Urine examinations for Bence Jones protein were negative on repeated oc-

casions. Corrected sedimentation rates were continuously elevated, ranging between 15 to 35 mm. per hr. A bone marrow, performed on February 19, 1959, demonstrated a hyperplastic marrow with occasional "grape cells" and "Mott cells." The spherules were not stained by PAS and Sudan III stains. Serum electrolytes of sodium, potassium, chloride and carbon dioxide as well as an oral glucose tolerance test, liver function studies, serum calcium, serum uric acid, were all within accepted ranges. Serial serum protein concentrations are summarized in Table 1.

TABLE 1.—CASE 3. THE LEVEL OF THE SERUM PROTEINS

	Total Protein in gm. %	*A*	A_1	A_2	*B*	*G*
1–5–59	6.6	3.55				3.05
1–13–59	7.15	3.55				3.6
1–20–59	6.74	2.3	0.46	1.55	0.81	1.62
2–10–59	6.75	3.55				3.2
2–26–59	7.75	3.4				3.35

Febrile agglutination for typhoid O and H, paratyphoid A and B, proteus OXK, OX19, OX2, and brucella were negative. C-reactive proteins were positive. Skin tests for histoplasmosis and coccidioidomycosis were negative, but PPD #1 produced a 10 mm. induration. Blood cultures drawn during a febrile episode were negative. Studies of the spinal fluid were within normal limits. Repeated latex agglutination tests were weakly positive. Throat cultures yielded a *Diplococcus pneumoniae;* however, cultures of the fluid taken from the left knee were entirely negative. Antistreptolysin and antihyaluronidase titers were 256 Todd units and 192 T. units respectively, but repeat studies exhibited no increase.

Course. The patient was observed only for the first 48 hours of hospitalization, following which he was given aspirin, gr. 10, every 4 hours, with dramatic relief. When the aspirin was discontinued the symptoms reappeared. The rheumatologist thought the most likely explanation for this man's disease was a form of atypical rheumatoid arthritis. The patient was discharged with instructions to take aspirin whenever he developed joint manifestations.

COMMENT. This marrow exhibited "grape cells" and Mott cells" despite the fact that he did not have hyperglobulinemia. The total protein and albumin/globulin ratios merely indicated a high normal globulin. Zlotnick[10], in his 8 cases reported a patient with carcinoma of the thyroid having an albumin/globulin ratio of 1:1. The remaining cases had reversed albumin/globulin ratios.

CASE 4. This 42-year-old white man was admitted to the U.S. Naval Hospital, Philadelphia, on March 24, 1959, with the complaints of weakness and fatigue. Events leading to his present illness commenced in February, 1956, when he complained of postprandial epigastric distress. Operation was performed for a "tumor" of the lower esophagus and the patient remained well for the next 2 years except for weakness and fatigue. Anemia of unknown etiology, accompanied by frequent, black, tarry stools, was noted in November, 1958; for this, the patient had received a total of 22 units of blood. On admission, the patient reported a weight loss of 30 lbs. during the preceding 2 years.

Physical examination revealed a temperature of 101.6° F., pulse of 100 per minute and blood pressure of 100/68. There was generalized pallor. Further examination showed a left thoracotomy scar, decreased vocal and tactile fremitus at the left lung base, grade III-IV harsh systolic murmur heard parasternally at the 4th and 5th interspaces, tender hepatomegaly 3 cm. below the right costal margin, 1+ pitting ankle edema, and shotty axillary and inguinal lymphadenopathy.

Laboratory studies including urinalysis, alkaline phosphatase, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, blood urea nitrogen, fasting blood sugar, VDRL serology and prothrombin time were within normal limits. A total serum protein was 5.15 gm.%, albumin 3.25

gm.% and globulin 1.9 gm.%. Stools tested with guaiac were repeatedly strongly positive. The initial complete blood count revealed a leukocyte count of 29,650 per c.mm., with 92% neutrophils, 5% lymphocytes, and 3% bands. The hemoglobin was 5.15 gm. per 100 ml. with a 19% hematocrit. After four units of blood, the hemoglobin was 10.5 gm. per 100 ml. and the hematocrit was 34%. A BSP revealed 9.75% retention in 45 minutes. Chest roentgenogram showed elevation of the left hemidiaphragm and pleural reaction at the left lung base. An upper gastrointestinal series demonstrated resection of the distal portion of the esophagus with anastomosis to the stomach. Multiple filling defects in the stomach were noted, which were thought to show infiltrating lesions. A bone marrow revealed hyperplasia of all three cellular elements with some evidence of megaloblastoid changes. Also, occasional "grape cells" with pale blue staining spherules were noted.

Course. The patient was transfused with 2000 ml. of whole blood and his symptoms of fatigue and weakness receded. Because of his subjective improvement, the patient signed out of the hospital despite medical advice to the contrary.

COMMENT. The large volume of blood received by this patient was most likely the factor causing the A/G ratio to appear normal. The interesting feature of this case lies in the fact that the numerous transfusions did not suppress "grape cell" formation. This might suggest that the formation of these cells in the marrow was dependent upon extremely small quantities of substances in the patient's blood, or dependent upon exogenous materials in the transfused blood to which his marrow responded with "grape cell" production. Also, it could be explained on the basis of biological inertia. Once the process was initiated, it took time before all "grape cells" were entirely eliminated from the marrow.

A REVIEW OF BONE MARROWS IN MULTIPLE MYELOMA. In addition to the 4 previous cases, a review of the bone marrows of 22 patients with proven multiple myeloma revealed that 17 of the marrows were entirely negative for any type of intracellular inclusion bodies. Four specimens demonstrated small, clear inclusions, but these were not of the "Mott" or "grape cell" variety. One case had "Mott cells" with intranuclear and intracytoplasmic spheroids but no "grape cells" (Fig. 2).

Discussion. Intracellular spheroid bodies in plasma cells have been the source of discussion in the medical literature since William Russell[5], in 1890, first described Russell bodies as the "characteristic organism of cancer," though they have since been shown in many chronic infections and granulomata (Pearse[4], White[8]). The spheroids of the Russell bodies were, however, acidophilic hyaline bodies and always PAS positive as opposed to the "Mott cell" and "grape cell" spherules which were PAS and Sudan III negative.

In 1905, Mott[3] described "his" inclusion body, which he observed in the cerebrospinal fluid, meninges and brains of patients with terminal trypanosomiasis. Since then the cell has been found in numerous other conditions such as typhus, malaria, kala-azar, myeloma and Waldenström's macroglobulinemia. Zlotnick[10] thought that the "Mott cells" were of protein nature, in that they did not stain with Sudan black (for fats) or with iodine and PAS (for carbohydrates); Bessis[1], however, stated that "Mott cells" contained glycoproteins, which stained red with fuchsin.

The "grape cell," described by Stich, Swiller and Morrison[7] in 1955, was thought to be different from the "Mott cell" because of its staining characteristics. Other investigators (Kingsley[2], Pearse[4]), however, were of the opinion that the "Mott cell" and the "grape cell" were similar. Recent studies in rabbits by Zlotnick, Gerichter and Nir[11] linked "grape cells" with the process of immunization. We reasoned,

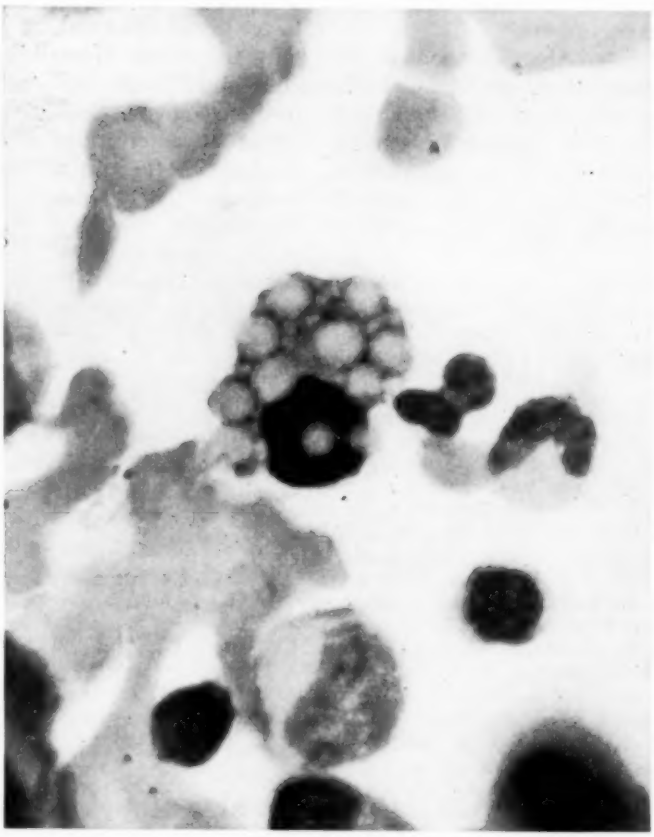

Fig. 2.—"Mott cell" with both extranuclear and single intranuclear clear spheroid bodies. (×950)

however, that although immunization may have played an important role, other etiologic possibilities were suggested.

From these case reports and from the brief discussion of the literature, it is apparent that Russell bodies, "Mott cells," and "grape cells," have broad spectrum diagnostic implications.

Finally, because of the wide difference of opinion concerning these cells, the authors advocate that a description of the cell containing inclusion bodies be made as to morphological characteristics, special staining properties and coexistent serum electrophoretic and ultracentrifugation findings.

Summary. In support of Zlotnick's previous paper concerning the presence of "grape" and "Mott cells" in entities other than multiple myeloma, 3 additional cases are reported as well as an unusual case of myeloma.

In addition, the bone marrows of 22 patients with multiple myeloma were reviewed by the authors. Four showed small inclusions; one, revealed intranuclear and intracytoplasmic, large, clear spheroid inclusions. The remain-

ing were entirely negative for intracytoplasmic inclusions.

It is suggested that ultracentrifugation or electrophoretic studies, or both, be obtained on patients exhibiting cell abnormalities as in the cases presented, since these inclusion bodies are seen in association with elevated and abnormal gamma globulins. Since various types of spheroid inclusions in plasma cells have been observed, it is suggested that the terms Russell bodies, "Mott cell" and "grape cell" be discouraged in favor of morphological and histochemical descriptions combined with electrophoretic and ultracentrifugation findings.

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SUMMARIO IN INTERLINGUA

Corpores Spheroide in Plasmocytos

In supporto del previe communication per Zlotnick con respecto al presentia de "cellulas racemiforme" e "cellulas de Mott" in entitates altere que myeloma multiple, 3 casos additional es reportate e etiam un caso inusual de myeloma.

In plus, le medullas ossee de 22 patientes con myeloma multiple esseva revistate per le autores. Quatro monstrava micre inclusiones; un revelava grande clar inclusiones spheroide intranucleari e intracytoplasmic. Le alteres esseva completemente negative pro inclusiones intracytoplasmic.

Es proponite que studios ultracentrifuge o electrophoretic o ambes sia obtenite in le casos de patientes qui exhibi anormalitates cellular como in le casos del presente reporto, proque le corpores de inclusion hic discutite se incontra in association con augmentate e anormal globulinas gamma. Viste que varie typos de inclusion spheroide in plasmocytos ha essite observate, le suggestion es presentate que le terminos "corpores de Russell," "cellula de Mott," e "cellula racemiforme" es discoragiate in favor de descriptiones morphologic e histochimic, in combination con constatationes de electrophorese e ultracentrifugation.

RECOGNITION OF RIGHT AURICULAR THROMBOSIS BY NEGATIVE CONTRAST ROENTGENOGRAPHY

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The source of a pulmonary embolus is frequently difficult, if not impossible, to establish with certainty during life. If peripheral thrombophlebitis is present, it is reasonable to assume that this is the origin of the embolus. Such an assumption becomes less reasonable and possibly erroneous when there is heart disease harboring perhaps an additional thrombotic focus.

Intracardiac thrombosis can be recognized by the technique of venous angiocardiography (Soloff and Zatuchni[4]). This method of study, however, may not be available. Or, there may be a justifiable reluctance to use such a procedure in a person who is gravely ill. Because of the simplicity, safety and availability of negative contrast roentgenography (Durant *et al.*[1]), and because such a technique might uncover right atrial thrombosis, as reported by Scatliff, Kummer and Janzen[3], it occurred to us to use this procedure in an attempt to determine its usefulness in a problem of this kind.

Case Report. L.K., a 34-year-old white man, was admitted to Episcopal Hospital on January 21, 1961, because of persistent hemoptysis and increasing heart failure. He was in Episcopal Hospital from December 14, 1959, through January 16, 1960, because of an acute anterolateral myocardial infarction, during which he also had a cerebral embolus producing transient aphasia and right hemiparesis. He was re-admitted to Episcopal Hospital on June 10, 1960, because of multiple pulmonary emboli with infarctions of the right middle and both lower lobes, and thrombophlebitis of the legs manifested only by calf tenderness. Although his course was stormy, he recovered and was discharged on June 29, 1960. Shortly thereafter, he again developed cough productive of bloody expectorate. In addition, he occasionally experienced pain in the loins. Although pulmonary and renal emboli were suspected, repeated chest roentgenograms showed no parenchymal abnormality and urinalyses were negative for blood.

A cardiac regimen, instituted one year previously, was continued and intensified, and elastic stockings were worn. In addition, anticoagulant effect was maintained at satisfactory levels. Notwithstanding such measures, his symptoms continued, and hepatomegaly and edema increased. He sought the advice of another physician who suggested ligation of the inferior vena cava to block emboli to the lungs from the veins of the legs.

Examination revealed a well developed male who did not appear ill other than for pallor. The jugular veins were slightly distended and pulsatile. The heart was enlarged to the left and the cardiac impulse was paradoxical. On inspiration, there became audible, at the left lower parasternal region, a protodiastolic gallop and a systolic regurgitant murmur. P2 was slightly increased and was louder than A2. The rate and rhythm were normal. The lungs were clear. The liver was enlarged and tender. There was symmetrical, pitting edema of the legs, and the calves were tender.

Electrocardiogram showed marked right axis deviation, a Qr complex in lead aVL

and essentially QS complexes in leads V4 to V6 with elevation of the ST segment and inversion of the T wave. The findings were interpreted, in the absence of change, as due to extensive healed anterolateral myocardial infarction with aneurysm formation.

Laboratory studies disclosed normal transaminase values, negative urinalysis and slight hyperbilirubinemia.

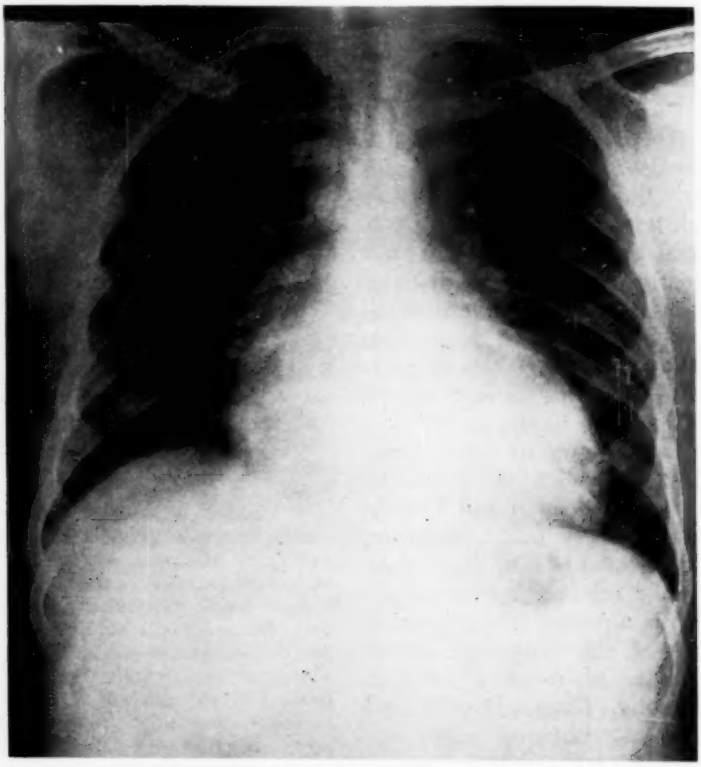

Fig. 1.—Conventional chest roentgenogram in the posterior-anterior projection

Conventional chest roentgenogram (Fig. 1) showed no abnormal pulmonary parenchymal density. The cardiac silhouette was increased in size and the pulmonary vascular markings were less prominent than normal.

A cardiac regimen was intensified and diuresis occurred. Nevertheless, there remained an irritating cough sometimes productive of bloody expectorate.

Negative contrast roentgenography was done on January 26, 1961. One hundred milliliters of carbon dioxide were rapidly injected into the left antecubital vein. The patient stated that during this procedure he noticed only a bubbling sensation along the vein. With the patient remaining in the left lateral decubitus position, a roentgenogram was taken immediately after the injection (Fig. 2) and again as rapidly as the casette could be changed (Fig. 3).

In Fig. 2, there is radiolucency within the superior vena cava and right atrium. The visualized superior vena cava is thin as is its margin which are normal findings. The right atrium appears enlarged. It lateral border is convex outward and 3 mm. thick, excluding pericarditis and effusion. In the region of the upper part of the right atrium, there is an area of increased density which extends medially and superiorly, outside of the confines of the right atrium. This area of density is further increased in the negative contrast roentgenogram taken shortly following the first one (Fig. 3). We interpreted

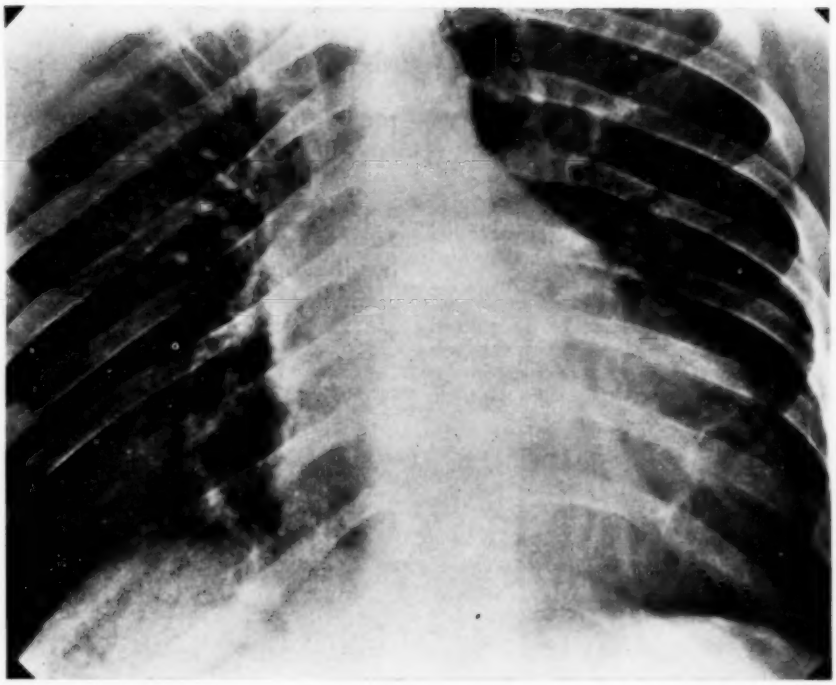

Fig. 2.—Negative contrast roentgenogram taken immediately after intravenous injection of carbon dioxide with the patient in the left lateral decubitus position. Note the increased density in the region of the upper part of the right atrium extending medially and superiorly, interpreted as due to right auricular thrombosis.

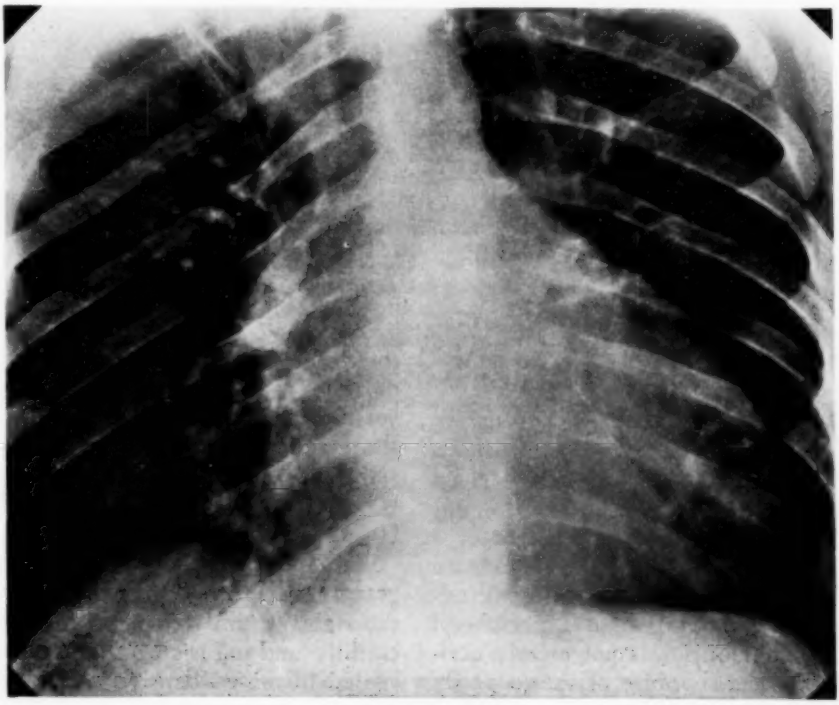

Fig. 3.—Negative contrast roentgenogram taken as quickly as possible after the first one. The density produced by right auricular thrombosis is increased.

these findings to indicate thrombosis of the right auricle.

The condition of the patient remained unchanged until January 31, 1961, at 3 a.m., when he was awakened by retrosternal pain and dyspnea. He was pale and sweaty, and blood pressure was unobtainable. He died shortly thereafter.

At necropsy, done by Dr. Allan Wallis, the right auricle was found to be thrombosed (Fig. 4). Otherwise, the right heart was free of thrombi. The heart was enlarged, including the right atrium. The left ventricle showed an extensive, healed anterolateral myocardial infarction, with aneurysm and mural thrombosis, due to occlusive disease of the anterior descending branch of the left coronary artery. Finally, there were infarcts in the inferior portion of the right middle lobe and left kidney.

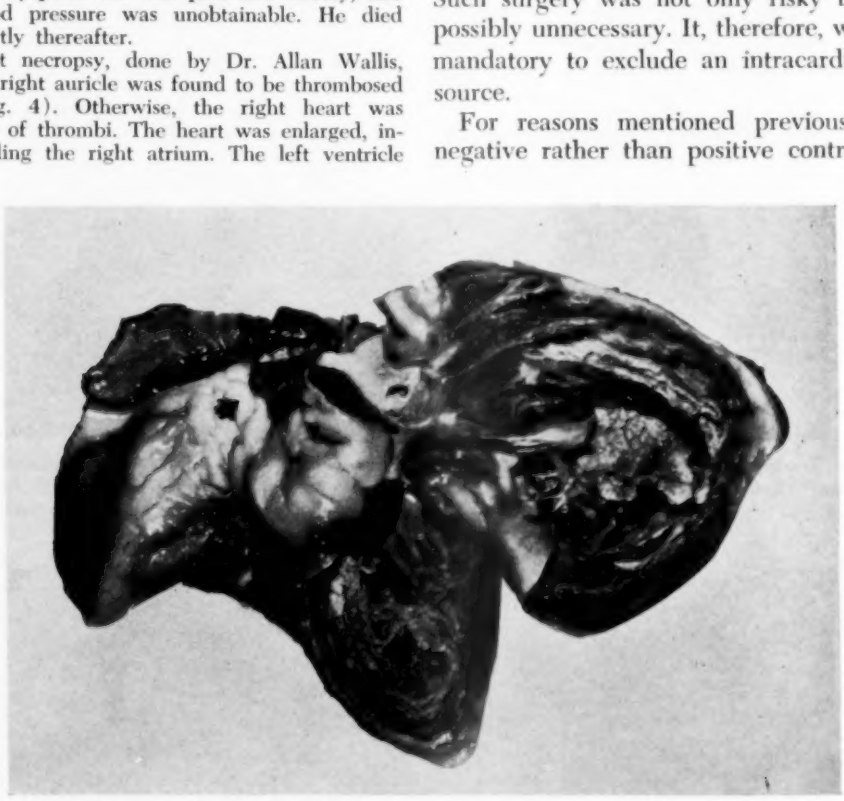

Fig. 4.—The heart at necropsy. The left ventricle is unroofed and is at the right. The arrow points to the thrombosed right auricle.

Discussion. The determination of a possible cardiac source for pulmonary embolism in the presence of both advanced heart disease and peripheral thrombophlebitis was not merely curiosity. In fact, because of the jeopardy produced by continued pulmonary emboli, in the presence of optimum anticoagulant effect, the suggestion was made to ligate the inferior vena cava. Such surgery was not only risky but possibly unnecessary. It, therefore, was mandatory to exclude an intracardiac source.

For reasons mentioned previously, negative rather than positive contrast roentgenography was chosen. Carbon dioxide was rapidly injected intravenously with the patient in the left lateral decubitus position. It was simple to do, and it produced no adverse effect. Roentgenograms were taken with conventional apparatus.

The negative contrast roentgenograms demonstrated enlargement of the right atrium, and absence of pericarditis and effusion. These also revealed increased density in the region

of the upper part of the right atrium extending medially and superiorly. The location and size of this area of increased density coincided with that of a thrombosed right auricle found at necropsy.

The area of increased density was not recognized in the conventional chest roentgenogram. However, in retrospect, there does seem to be increased density within the cardiac silhouette corresponding in location with that found on the negative contrast roentgenograms. But, even if recognized, it probably would be interpreted to indicate left atrial enlargement rather than right auricular thrombosis because of apparent continuity with a similar area of increased density on the left side.

In contrast to the difficulties in recognition and interpretation of the findings on the conventional roentgenogram, the area of increased density was readily observed following injection of carbon dioxide. The right atrium was now radiolucent and decreased in density which allowed for apparent increase in density produced by right auricular thrombosis. In short, the silhouette sign (Felson and Felson[2]) was abolished by carbon dioxide.

In the absence of lesions of the right auricle, negative contrast roentgenograms show radiolucency from the superior vena cava to the right atrium. Surrounding or intervening density, if it occurs, is homogeneous, soft in appearance and like that of the left ventricle or less.

Increase in density can be produced by lesions other than right auricular thrombosis and must be excluded. An intrinsic right atrial lesion was considered unlikely because of preservation of the outline of superior vena cava within the right atrium, absence of change of lateral contour and extension of density medially and superiorly. Lifting the patient towards the erect position might have been of additional value in excluding a right atrial lesion.

Left atrial density would appear within the right atrial gas shadow (Scatliff, Kummer and Janzen[3]). Other possibilities like pleural effusion and adjacent pulmonary parenchymal abnormality were not present. The descending branch of the right pulmonary artery was lateral and also inferior to the major portion of the density. Finally, the right superior pulmonary vein would not be of the size, shape or location observed.

In the only report which we could find of the recognition of thrombosis by negative contrast roentgenography, Scatliff, Kummer and Janzen stated that such a lesion produces an abnormal outline in the opaque band surrounding the right atrium[3]. In their case, the superior arc of the band was of abnormal caliber, and the summit and inferior arc were normal in size. It is possible that the widening of the superior arc described but not illustrated by them is due to superimposed density as observed in the case reported herein. Regardless, these findings indicate that negative contrast roentgenography can uncover a thrombosed right auricle. For this purpose, this technique might be more advantageous than positive contrast roentgenography, because increased density produced by the former would be obscured by the latter, and also because lack of filling of the right auricle by opacifying agents does not necessarily indicate occlusive disease.

Summary and Conclusions. A case is reported of a 34-year-old man gravely ill with advanced coronary artery disease, persistent pulmonary emboli and peripheral thrombophlebitis. In an attempt to exclude an intracardiac thrombotic source, the tech-

nique of negative contrast roentgenography was employed because of its safety and simplicity. A thrombosed right auricle was found, and confirmed, and was manifested in the negative contrast roentgenograms by increased density of the right auricle, not otherwise recognized.

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SUMMARIO IN INTERLINGUA

Recognition de Thrombose Dextero-Auricular per Roentgenographia a Contrasto Negative

Es reportate un caso de un masculo de 34 annos de etate, gravemente malade con avantiate morbo de arteria coronari, persistente embolos pulmonar, e thrombophlebitis peripheric. Pro excluder le possibilitate de un fonte thrombotic intracardiac, le technica de roentgenographia a contrasto negative esseva empleate in consideration de su innocentia e simplicitate. Un thrombotisate auricula dextere esseva discoperite, e confirmate, manifeste in le roentgenogramma a contrasto negative per un augmentate densitate del auricula dextere, non alteremente recognoscite.

SUMMARIO IN INTERLINGUA

(See page 87 for original article)

Magnesium del Sero e Arrhythmias Cardiac con Referentias Special al Intoxication per Digitalis

Le valores seral de Mg^{++}, Ca^{++}, e K^{+} esseva determinate in 45 patientes con varie typos de arrhythmia cardiac. Le valor medie de magnesium seral de 1,43 ± 0,19 mEq/L non esseva significativemente differente ab le valor medie de 1,6 ± 0,20 mEq/L trovate in normales. Nulle relation esseva trovate inter le nivello de magnesium seral e le typo de arrhythmia.

Intoxication per digitalis esseva presente in 21 patientes. Le nivellos seral de magnesium esseva significativemente plus alte post le correction del syndrome de intoxication, ben que le ingestion de magnesium non esseva supplementate in ultra de illo ordinarimente trovate in le dieta. Le basse nivello seral de magnesium esseva probabilemente secundari al reducite ingestion de alimentos e consequentemente al basse ingestion de Mg^{++} durante le periodo de disfallimento congestive e al diurese inducite durante le therapia del disfallimento congestive. Le possibilitate de un transferimento intra-extracellular o de un alteration del fraction ligate de Mg^{++} in le sero non pote esser evalutate a base de iste datos.

SERUM MAGNESIUM AND CARDIAC ARRHYTHMIAS WITH SPECIAL REFERENCE TO DIGITALIS INTOXICATION

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The relation between intra- and extracellular cation concentration determines the membrane potential of the resting or contracting cardiac muscle fiber. Potassium is the cation present within the cells in highest concentration and changes in amount of this ion are frequently accompanied by cardiac arrhythmias. Magnesium is present in the cells in amounts second only to potassium. Little information is available concerning the relation between cardiac function and serum magnesium concentrations. In the dog, large doses of magnesium salts, given intravenously, will delay atrioventricular and intraventricular conduction time and convert ventricular tachycardia produced by barium chloride or strophanthedin to a sinus rhythm (Miller and Van Dellen[11], Rothberger and Zwillinger[13], Smith, Winkler and Hoff[14], Stanbury and Farah[15]). Stanbury and Farah, using a denervated heart lung preparation found the rate of sino-auricular conduction was slowed proportionately to the magnesium concentration in the perfusate[15]. Because of this apparent depressant effect of magnesium on cardiac conduction, patients with cardiac arrhythmias, including those due to digitalis intoxication, have been treated with magnesium salts (Boyd and Scherf[1], Enselberg, Simmons and Mintz[4], Stanbury and Farah[15], Szekely[16]). The results of previous studies were inconclusive although in several patients the cardiac rhythm was restored to normal. It is not clear from the reported studies whether magnesium deficit originally existed in the patients with arrhythmias and magnesium administration was replacement therapy, or whether serum levels were normal and changes in cardiac conduction represented the effects of excessive amounts of magnesium. The present study was designed to determine if there is a relation between serum magnesium level and cardiac arrhythmia.

Methods. Patients were selected for study on the basis of electrocardiographic evidence of an arrhythmia. Patients with disease frequently associated with abnormalities of Mg^{++} metabolism such as delirium tremens, long maintenance on intravenous feeding, or renal failure were excluded from the study.

Patients with congestive heart failure were included if the blood urea nitrogen was within normal range. The diagnosis of digitalis intoxication was made on the basis of a history of taking the drug, symptoms, electrocardiographic evidence of drug effect, and improvement in symptoms and electrocardiographic changes after discontinuation of the drug.

Serum Mg^{++} and Ca^{++} determinations were done by the sodium ethylenediamine tetracetate titration method as described by Carr and Frank[2]. Serum potassium was measured by standard flame photometer techniques. Electrocardiograms were always obtained at the time serum samples were drawn.

ions and the type of arrhythmia present.

Digitalis intoxication was present in 21 patients and was a major cause of the arrhythmias observed. Table 2 lists pertinent clinical data, serum magnesium, calcium and potassium concentrations obtained from the study of these patients. Eighteen were males and 3 were females. The duration of digitalis intoxication could not be reliably evaluated in 10 patients. The remaining 11 patients had been intoxi-

TABLE 1.—SUMMARY OF CLINICAL AND ELECTROCARDIOGRAPHIC DATA FROM PATIENTS WITH ARRHYTHMIA

		Type of Arrhythmia				
Etiology of Heart Disease	**Total Patients*	*Premature Atrial Contractions*	*Supra-ventricular Tachycardia*	*Atrial Flutter or Fibrillation*	*Conduction Defect*	*Ventricular Premature Contractions*
ASHD	25	5	4	10	8	4
RHD	9	1	0	2	4	3
HCVD	6	1	1	2	2	0
Secondary to Lung Disease	2	0	0	1	1	0
†Miscellaneous	4	0	1	3	2	0

*Eleven patients had more than one arrhythmia.
†Includes a patient with myocarditis, one patient with atrial septal defect and 2 patients with atrial fibrillation of undetermined etiology.

Results. Forty-six patients have been studied. Table 1 lists the types of heart disease and the observed arrhythmias in the patients studied. The mean serum magnesium was 1.43 ± 0.19 mEq. per L. The normal serum magnesium in our laboratory is 1.60 ± 0.20 mEq. per L. Although the mean of the patient group was less than our normal, the difference was not significant. There was no relation between the type of arrhythmia and the serum magnesium level. The mean serum calcium was 4.59 ± .25 mEq. per L. and potassium 4.3 ± .69 mEq. per L. as compared to normals of 4.8 ± .3 mEq. per L. and 4.4 ± .3 mEq. per L., respectively. Again there was no relation between the serum level of these

cated with digitalis for an average of 3.3 days with a range of 1 to 7 days. Fifteen patients had received diuretic therapy. Chlorothiazide was the most frequently used diuretic. Thirteen had responded with a diuresis and weight loss of 5 to 10 pounds within a 3-day period.

The mean serum magnesium level prior to correction of the digitalis intoxication was 1.38 ± 0.13 mEq. per L. After correction of the intoxication syndrome mean serum magnesium rose to 1.58 ± 0.16 mEq. per L. Serum K^+ values rose from a mean of 4.11 ± 0.79 mEq. per L. to 4.41 ± .41 mEq. per L. and serum calcium levels fell from a mean of 4.55 ± .23 mEq. per L. to 4.36 ± 0.16 mEq. per L. The differ-

ence between the mean levels of these ions before and after therapy was significant at the 0.001 level (Croxton[3]).

None of these patients exhibited the central nervous system signs and symptoms that have been reported to be associated with severe depletion of total body magnesium (Flink *et al.*[5], Hammarsten and Smith[6]).

Discussion. The depolarization and repolarization of cardiac muscle and conduction system fibers are dependent upon the relative concentrations of various ions on either side of the cell membrane (Hecht[7]). There is little evidence as yet to determine whether or not metabolic membrane alteration brings about functional cardiac change by alteration of ion gradients between inside vs. outside, or whether these effects are mediated by a change in rate of passage of ions through the membrane. In either event relative changes in potassium ion concentrations appear to be most closely related to the depolarization-repolarization process. Since magnesium concentration within the cell is second only to that of K^+, it is reasonable to assume that this cation might also play an important role in the process. There is no direct evidence to support this concept. Evidence to date indicates the primary role of magnesium as a cofactor in enzyme systems concerned with glycolysis and the degradation of fatty acids that are used for energy purposes (Muntz[12]).

The data presented here demonstrate that in patients with arrhythmias due to digitalis intoxication the serum levels of Mg^{++} and K^+ are diminished prior to therapy when compared with the concentrations measured after therapy. This change would suggest similar changes might occur within the cell. Considerable evidence is available to indicate that low intracellular potassium levels do occur in association with digitalis intoxication (Lown and Levine[9]).

Several mechanisms could account for lowered serum magnesium level: 1) decreased intake, 2) increased output in the urine and feces, 3) a shift from the extracellular compartment into the cells or 4) a shift from associated to dissociated complexes. Food intake is diminished in patients severely ill with congestive failure. Diminished food intake and thus diminished magnesium intake could be a factor in producing the low levels of this ion found in our patients. Patients maintained on intravenous fluids for a prolonged period develop a negative magnesium balance (Flink *et al.*[5], Hammarsten and Smith[6]).

It is more reasonable to assume the lower serum levels observed were secondary to excessive urinary loss through diuresis. Martin, Mehl and Wertman reported a marked decrease in serum magnesium levels during the period of diuresis in 10 patients with congestive failure[10]. Hills *et al.* observed that magnesium excretion was dependent on sodium chloride excretion[8]. More specifically as urinary chloride increased, urinary magnesium increased, while potassium and magnesium excretion were unrelated. Increased sodium chloride excretion occurs during diuresis and this is likely the mechanism whereby serum magnesium was lowered in our patients with digitalis intoxication. Fifteen of the 21 patients with digitalis intoxication were on diuretics and 13 lost weight. No data are available from our patients to determine if intracellular-extracellular shifts of magnesium occurred or if there was a change in the amount of magnesium bound to protein.

The significance of the decreased extracellular Mg^{++} in patients with digitalis intoxication is unknown. Since other investigators (Boyd and Scherf[1],

TABLE 2.—SERUM MAGNESIUM, POTASSIUM AND CALCIUM VALUES IN PATIENTS DURING DIGITALIS INTOXICATION AND AFTER RECOVERY

Patient	*Etiology of Heart Disease*	*Arrhythmia Present*	*Serum Electrolytes in mEq./L.* Mg^{++} *Before*	Mg^{++} *After*	K^{+} *Before*	K^{+} *After*	Ca^{++} *Before*	Ca^{++} *After*	*Diuresis*
1	ASHD	Tachy. A.F.	1.31	1.54	4.6	3.9	4.52	4.51	Yes
2	ASHD	Tachy.	1.59	1.70	3.6	4.8	4.34	4.40	Yes
3	ASHD HCVD	Wenckebach's Tachy.	1.31	1.50	4.7	4.5	4.22	4.24	Yes
4	ASHD	1° block	1.29	1.59	4.2	4.5	4.21	4.00	Yes
5	RHD	2:1 Flutter 1° block	1.72	1.63	6.4	5.8	4.22	4.23	Yes
6	ASHD Infarct	1° block VPC, Tachy.	1.24	1.81	3.2	4.1	4.38	4.28	Yes
7	ASHD	Bigeminy 1° block	1.59	1.86	5.2	4.3	5.00	4.56	Yes
8	ASHD	LBBB Tachy	1.36	1.69	4.0	4.6	4.35	4.30	No
9	ASHD	APC							

8	ASHD	LBBB Tachy	1.36	1.69	4.0	4.6	4.35	4.30	No
9	ASHD HCVD	APC 1° block	1.35	1.49	3.8	4.2	4.79	4.35	No
10	HCVD	A.F. 3:1 Flutter	1.33	1.36	3.6	4.0	4.80	4.60	Yes
11	RHD	VPC APC	1.13	1.57	3.2	4.6	4.68	4.51	No
12	RHD	A.F.	1.37	1.41	3.8	3.9	4.75	4.38	No
13	RHD	1° block	1.47	1.56	4.2	4.1	4.62	4.47	Yes
14	RHD	VPC	1.40	1.68	5.0	4.6	4.43	4.21	No
15	RHD	VPC 1° block	1.21	1.44	4.4	4.6	4.64	4.20	Yes
16	ASHD	VPC APC	0.90	1.28	3.2	4.1	4.68	4.52	Yes
		Complete block	1.39	1.50	3.4	4.6	4.50	4.46	No
18	HCVD	LBBB	1.56	1.83	4.5	4.2	4.36	4.30	Yes
19	ASHD	1° block	1.29	1.56	4.1	4.3	4.86	4.64	No
20	HCVD	A.F. 2:1 Flutter	1.24	1.72	3.2	4.6	4.56	4.39	No
21	RHD	A.F.	1.26	1.48	4.1	4.3	4.57	4.37	Yes

Carr and Frank[2], Enselberg, Simmons and Mintz[4], Stanbury and Farah[15], Szekely[16]) have shown transient improvement in arrhythmias due to digitalis overdosage when treated with magnesium and we have demonstrated a significant change in magnesium concentrations after restoration of a normal rhythm, further work seems indicated to determine the effect of magnesium on cardiac muscle membrane potentials and to evaluate further its role as an adjunct in the therapy of patients with digitalis intoxication and cardiac arrhythmias.

Summary. Serum Mg^{++}, Ca^{++} and K^{+} values were determined on 45 patients with various types of cardiac arrhythmias. The mean serum magnesium of 1.43 ± 0.19 mEq. per L. was not significantly different from the mean of 1.6 ± 0.20 mEq. per L. found in normals. There was no relationship between the serum magnesium level and the type of arrhythmia.

Digitalis intoxication was present in 21 patients. Serum magnesium levels were significantly higher after correction of the intoxication syndrome, even though magnesium intake was not supplemented beyond that ordinarily found in the diet. The low serum magnesium was probably secondary to decreased food intake and thus to low Mg^{++} intake during the period of congestive failure, and to diuresis induced during the therapy of the congestive failure. The possibility of an intra-extracellular shift or change in the "bound" fraction of serum Mg^{++} cannot be evaluated from this data.

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PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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IDIOPATHIC NEUROPATHY IN CANCER
A FIRST SIGN IN MULTIPLE SYSTEM SYNDROMES ASSOCIATED WITH MALIGNANCY

BY GEORGE W. HOLT, M.D.*

CANCER and vascular disease, often associated with neuropathy and polyneuropathy, are top ranking killers of man. These commonly affect and often destroy the nervous system. Their coexistence in the body and more importantly their possible synergism in common neural lesions raise certain questions: 1) are the relationships between cancer and vascular abnormality mainly fortuitous? 2) what are the relationships of common denominators in their pathogenesis and the production of neuropathy? Since neuropathy and polyneuropathy may be a first sign of malignancy associated with multiple system syndromes, answers to the above questions would be of value.

A vascular component in pathogenesis has been suggested in three most prevalent types of neural disease: diabetic, Landry-Guillain-Barré, and collagen polyneuropathies. Another of comparable incidence is idiopathic neuropathy of cancer, also called carcinomatous neuropathy. In multiple system vascular syndromes associated with the first three neuropathies, the neural symptom may be the first warning. This is likewise true in neuropathy of cancer.

Similarities in the characters of these four neuropathies pose a question of a vascular component in the pathogenesis of the idiopathic variety associated with malignancy. This type, as the name implies, is not caused by metastases, infiltration, or mechanical effects of neoplasm. The neuropathy relates to causes of, rather than to the presence of, cancer. In addition to a possible vascular component, there are other pathogenetic factors in idiopathic neuropathy of malignancy. Individual

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susceptibility or a diathesis may be a predisposing factor. Neuropathy in general may result from cumulative factors[75]. These may also contribute. It would appear that the arteriole and small blood vessels participate in hypersensitization. This may be a pathogenetic factor. Reactive, reparative, and autoimmune responses to malignancy, or to agents pathogenetic of malignancy may contribute to hypersensitization. The latter has been interpreted as an antigen-antibody reaction between foreign protein and the small blood vessels.

Dysfunction of nerve tissue and its vasa nervorum is referred to as neuritis. To this, physicians attribute paresthesia, pain, paralysis, and analgesia. In clinical usage neuritis may relate to toxic, traumatic, compressive, infectious, and post-infection immunopathologic affections of nerve. Often these abnormalities are partially or wholly inflammatory. This is predominantly interstitial, although parenchymatous involvements are commonly associated.

The major contributions to our knowledge of neuritis have come from clinical observations. Neuritic phenomena are frequently associated with major problems in clinical medicine. These problems include the care of pain syndromes, as they relate to the diagnosis, prognosis, and therapy of disease. Observation of neural mechanisms in the following syndromes: causalgia, neuralgia, zoster, tabes dorsalis, and polyneuropathy, aids in the understanding and management of neuropathy of cancer.

Causalgia, the burning pain syndrome, was described by S. Weir Mitchell. His Civil War monograph on ballistic injuries and the peripheral sensory nerve remains a classic. Causalgic pain produces physiologic and psychologic disturbances. His contribution established that minor injury to peripheral nerves, especially the median and posterior tibial nerve trunks, often produces major disability if not death.

The magnitude of disability of minor peripheral sensory nerve trauma should be judged on the basis of physiologic effect rather than morphologic defect. The affected extremity in burning pain syndrome presents dramatic physiologic changes. Neurotrophic, vasospastic, and hemodynamic phenomena collaborate in the production of shiny skin, tapered atrophy, nail growth failure, osteoporosis, hyperpathia, and lowered temperature. Sympathectomy relieves burning pain and vasoconstriction in many cases. Advancing physiologic devastation may also include dysfunction of more cephalad areas in the central nervous system and personality destruction. A minute lesion of integrity of the sensory neuron may impair effective intelligence. This is fundamental in neural phenomena, especially in the sensory hyperpathia, emotional chaos, and intellectual degradation of causalgia. The physiologic concept does not require metered data or verbal testing but is self evident to experienced observers of patients who have causalgia or similar disorders.

Neuralgia is paroxysmal lancinating pain in the distribution of a sensory nerve. The patient notes that the repetitive lancinating pains prevent any continuing acts of purpose. He also learns the pain is ameliorated by pressure massage. In trigeminal neuralgia the forehead may be denuded by rubbing.

Etiologic factors in neuralgia, a ganglionic disturbance, include virus infection of the ganglion cells, multiple sclerosis, malignant invasions, edema, ischemic vasculitis, compression, and unknown causes. The classic idiopathic neuralgias are characterized by hyperesthesia and hyperalgesia. These are prominent in the neuralgic distribution,

especially the trigger area. The cold spoon may activate the trigger and precipitate the pain of trigeminal neuralgia. Swallowing or talking is absolutely avoided in glossopharyngeal neuralgia. The reduction of peripheral stimuli lessens the frequency of the attacks. Pain or thermal fiber stimuli causes bambardment of the ganglion and the cells discharge, producing pain. The maximum severity of pain is immediately attained. These pains recur at approximately the same interval. The pain paroxysm may last 10 to 60 seconds and may recur every 5 minutes. Massaging appears to shorten afferent stimulation and bombardment. The duration and intensity of firing of the ganglion appears reduced. After-pain similarly is decreased. The patient may refer to the pain as shooting, sticking, or cutting. Attacks may occur during one season, undergo remission in the next, only to recur the following season.

Spiller proposed the first successful therapeutic attack on trigeminal neuralgia. He reasoned central sensory root section would interrupt afferent paths of the Gasserian ganglion and would render the neuralgic area painless. Complete denervation also produced analgesia and anesthesia and deactivated the trigger.

Section of trophic fibers to the cornea may cause ulceration. Incomplete denervation of the face may be followed by disquieting paresthesia. In symptomatic trigeminal neuralgia of cerebellopontine angle tumor severe pain may occur in a moderately hypalgesic area. The latter usually distinguishes symptomatic and essential tic douloureux.

Frazier performed the first Gasserian ganglion sections. This strategic and surgical achievement formed the basis for our present understanding of neuralgic pain and its direct abolishment. Sensory root section in glossopharyngeal neuralgia was another application of similar principle. Spiller also suggested section of the spinothalamic tract for the control of pain in cancer. The effectiveness of these procedures is indicated by the decrease of suicide in these conditions. Currently, alcohol injection also is used in the relief of trigeminal neuralgia.

Herpes zoster, a virus infection of cells of a posterior ganglion is distinguished by abnormalities of sensation and later dermatomal herpes. Once known as St. Anthony's Fire, dermatomal burning pain and prickly paresthesia distinguish the preherpetic phase. The period of herpetic vesiculation is accompanied by steady or lancinating pain and hypalgesia confined to particular parts of the dermatone rather than to the herpes. Zoster convalescence may be deranged by late neuralgia. Motor paralysis occurs only in recrudescence and spreading of the virus to the anterior horn cells. A spread from one sensory ganglion to the next is prevented by the extraspinal and extradural location of the ganglion. Once in the spinal cord, virus spread is usually a contiguous and unilateral motor affection. Multiple rather than single dermatome and bilateral rather than unilateral vesicular involvement suggests neoplastic infiltration of ganglia with secondary zoster infection.

Certain relationships of virus infection to cancer are of interest. These may be closely akin to problems of malignant neuropathy. In enigmatic unsolved problems of malignancy even distant factors are worth considering. It has been observed that lymphomatous invasion of multiple dorsal ganglia predisposes to corresponding herpes zoster virus infection. Zoster cutaneous lesions after healing may undergo malignant change. Basal and squamous cell carcinomas have been observed.

Wyburn-Masson[77] reported cancer in a pharyngeal area previously affected with the herpetic lesions of glossopharyngeal zoster. Schmidt[60] reported metastatic carcinoma in the herpetic vesicles of acute zoster. The author has observed metastatic carcinoma in the herpes of zoster in the 5th dorsal dermatome breast area in disseminated breast malignancy, 3 years after mastectomy and irradiation. These were the only cutaneous lesions. Metastases in herpes in an area of previous breast cancer, resection, and irradiation may have implications involving immunity, lymphatic spread, virus ganglionitis, and therapy. Guillain and associates[31,32] reported that zoster produced changes indistinguishable from rheumatoid arthritis and periarthritis in those digital joints adjacent to the cutaneous herpetic lesions.

Tabes dorsalis is characterized by lancinating and sticking pains. These probably are secondary to post infectious, inflammatory, and vascular changes in the posterior root and ganglion. Pain perception is delayed as the fast pain ganglion cells and fibers are destroyed. Only slow conducting pain neurons remain. Ataxia of stance and gait, especially in the dark or with the eyes closed, is a common sensory deficit. Clinicopathologic observation has long since established that dorso spinal atrophy is responsible for ataxia. The steps in pathogenesis of the tabetic lesion have not been clarified. Pathologic review of the nervous system in postdiphtheritic polyneuropathy suggests little about its pathogenesis and nothing about diphtheria except that the infection terminated prior to the neuropathy. Harvey *et al.*[36] have remarked the clinical and necropsy findings in disseminated lupus erythematosus may not correlate.

The syndromes, causalgia, neuralgia, zoster, and tabes dorsalis illustrate varieties of sensory hyperactivity and deficit including pain, paresthesia, analgesia, and ataxia. A knowledge of these is essential in understanding idiopathic neuropathy of malignancy. These syndromes exemplify selective vulnerability of sensory neural elements to virus, other infectious, morphologic, physiologic, metabolic, and unknown agents. Poliomyelitis and motor neuron disease are examples of selective vulnerability of motor elements. In certain neuropathies of malignancy, susceptibility of the nervous system may be generalized rather than selective. Host as well as disease factors may play a part.

Polyneuritis, in which sensory and motor abnormalities coalesce, illustrates combined symptoms and signs observed in idiopathic neuropathy of malignancy. Landry published in 1859 an early account of what continues to be known as acute ascending paralysis. It is of interest that his patient first noted paresthesia and mild pain of the feet and hands. As advancing paralysis ascended to the bulb, sensory deficit developed in the periphery of the extremities. The deficit was more severe in the feet. It is probable that early pain often is masked with analgesics. These also may fully upgrade an incipient paralysis of the respiratory mechanism. Later, failure of the pain mechanism as a result of disease renders analgesics unnecessary. Landry and many physicians since have emphasized the motor paralysis and minimized the sensory symptoms and signs. Bulbar and respiratory motor mechanism failure are responsible for the mortality. This accounts for the continued usage of Landry's term, acute ascending paralysis, in the presence of sensory nerve excitation and deficit. In 1892, Osler described this syndrome as acute febrile polyneuritis acknowledging sensory abnormality. He suggested an in-

fectious association and referred to it as a winter disease. In 1916, Guillain and associates, in polyneuritis, reported high cerebrospinal fluid protein, an important contribution. Guillain referred to this as an albumino-cytologic dissociation, a term of historical value today. Clinicopathologic observations including those of Haymaker and Kernohan[37] have suggested that the eponyms of Landry, Osler, and Guillain-Barré apply to polyneuritides which cannot be differentiated. Basically they may be facsimiles or identical. Polyneuritis frequently begins with paresthesia and pain. Often following these, motor paralysis develops. First foot drop and then wrist drop appear. Paralysis then ascends the extremities and involves the bulb. Sensory deficits: analgesia, anesthesia, and ataxia, are usually late signs[44,45]. This sequence of polyneuritis is common in ischemic neuropathy and polyneuropathy[45]. Factors which might favor this sequence include relative sensitivity of neural tissue to anoxia and ischemia, length of neuron, inadequate peripheral collateral circulation, vasospasm, and others.

Since World War I clinical interest in neuritis has broadened to noninflammatory affections. These are termed neuropathy or polyneuropathy. An enlightened awareness of neuropathy is concerned with nerve impulse formation and transmission and its breakdown. Nerve impulse failure, now conceived of chemically and physically, is being related to neuropathies resulting from vitamin deficiency, metabolic abnormality, chemical defects, arteriolar ischemia and immune reactions. Current knowledge of pathogenesis is insufficient to explain nerve impulse failures. Hence specific therapies are unknown.

Idiopathic neuropathy may be associated with diabetes mellitus or prediabetic state, post infection immunopathologic states, and collagen vasculitis. Additional causes of polyneuropathy include porphyria, heavy metal intoxication, and alcoholism. Exposure to insecticides, fungicides[11], and weed killers[12] may produce serious neural disorders.

Early polyneuropathy in an ambulatory patient is recognized by neurologic history and examination. When paralytic manifestations are acute, severe, or advancing, respiratory emergencies are anticipated. Nevertheless, today in seriously ill patients certain components of the illness, as chills and fever, drugs or psychosis, may mask advancing paralysis. Sensory ganglion pain in the chest, neurogenic atelectasis, and respiratory failure, common in polyneuropathy, may be confused with pneumonia. The distended paralyzed bladder and abdominal ganglionic pain near McBurney's area may be mistaken for appendiceal abscess. In such cases the need for neurologic evaluation may not be recognized. As a result a neural lesion may progress unnoted. This is indeed likely if more than one system is affected, as in gastric cancer associated with polyneuropathy.

If diagnostic thinking is restricted to a single pathogenetic mechanism or permitted to conclude with establishment of a single diagnosis, only the more prominent of two interrelated clinical syndromes may be recognized. In known cancer the development of signs of a neural lesion is often a result of metastases[2,16,64]. In polyneuropathy accompanying multiple myeloma, disseminated lymphoma, and allied malignancies, careful clinical and pathologic examination of the peripheral nerves should be made to establish the presence or absence of metastatic infiltrations[4]. Pseudopolyneuropathy may describe the initial clinical picture in disseminated malignant infiltration of the peripheral nerves, roots, ganglia,

cord, and brain. In multiple myeloma and disseminated lymphoma a polyneuropathy of malignancy not associated with metastases or infiltrations may occur. In single myeloma and single lymphoma associated with polyneuropathy the latter is a neuropathy of malignancy. It is possible for polyneuropathy and pseudopolyneuropathy to have occurred in the same patient.

NEUROPATHIES OF CANCER. In idiopathic neuropathy the possible association and interrelationship with an occult malignancy are important clinical considerations. Reports have been increasing in the last 50 years of neural abnormality associated with localized cancer. Pathogenetic factors may predetermine cancer. Simultaneously these factors may contribute to the production of an advanced neuropathy. An essential part of the multiple pathogenetic mechanisms of neuropathy of malignancy is that the neural syndrome may have developed, resolved, or terminated fatally prior to the appearance of any clinical evidence of malignancy. In 15 of 19 cases of idiopathic neuropathy of cancer, Henson, Russell, and Wilkinson[42] found neuropathy preceded malignancy. A temporal precedence in the natural history of neuropathy of cancer has special significance for the diagnostician. Thus idiopathic neuropathy deserves a circumspect and definitive diagnostic approach. Periodic reexamination for cancer over a number of years as well as neurologic re-evaluation is in order.

The malignancies associated with idiopathic neuropathy include carcinoma, lymphoma, reticulosis[46] and myeloma[67]. The frequent sites of malignancies have been lung, breast, gastrointestinal tract, ovary, uterus, rectum, prostate, lymph node, and bone marrow. First in incidence among the neoplasms of idiopathic neuropathy is bronchial carcinoma. This incidence may reflect the latter's prominence among cancers. Multiple types and sites of malignancy associated with idiopathic neuropathy suggest denominators common among the cancers in their relationship to neuropathy.

There are various types of neuropathy associated with cancer. One neural tract, function, or many are attacked. Occasionally the neuropathy presents as a single affection or as two or more components of a polyneuropathy. A mononeural affection may develop into a clinical picture of multiple or successive neuropathy or polyneuropathy. Often the neuropathy is a mixed form of sensory and motor abnormalities. Authors have suggested a schism in which cases conform to certain pathophysiologic or pathoanatomic descriptions. These include polyneuropathy, parenchymatous cortical cerebellar atrophy, proximal motor neuropathy, primary sensory neuropathy, subacute combined degeneration, secondary pellagra, and dementing encephalopathy. Wernicke's encephalopathy as well as Korsakoff's psychosis have been observed. An association of Wernicke's and Korsakoff's[1] lesions might be predicated on an anatomic basis. In 43 patients with carcinomatous neuropathy, Brain and Henson[8] found dementia in 14. Mental disturbances were prominent in other patients. Mongolism is said to have an expected frequency of leukemia three times that in the normal population[73]. This might suggest abstruse etiologic factors in certain neural abnormalities related to malignancy. The diversity of idiopathic neuropathies associated with malignancy proposes that most cases do not conform rigidly to pathoanatomic or pathophysiologic description.

A polyneuronal carcinomatous neuropathy has been described by Williamson[74], Weber and Hill[69], Wyburn-Mason[76], Brain[6], Heathfield and Wil-

liams[40], and Henson, Russell, and Wilkinson[42].

Primary sensory neuropathy has been documented by Denny-Brown[21], Wyburn-Mason[76], Kremer and Pratt[49], Dodgson and Hoffman[23], Gray, Woolf, and Wright[29], Smith and Whitfield[63], and Murdock and Walker[55]. Denny-Brown has reported detailed neuropathologic changes in primary sensory neuropathy. McAlpine and Page[54] have suggested that sensory neuropathy secondary to posterior root ganglion degeneration also may occur in the absence of carcinoma.

Proximal motor neuropathy has been described by Hart[35]. Mixed sensory and motor neuropathy, a common form of idiopathic neuropathy of malignancy, has been described by Heathfield[38], Lennox and Prichard[52], Elkington[25], Henson[41] Heathfield and Williams[40], and Jewesbury[47]. Heathfield and Williams[39] believe periarteritis nodosa is the difficult differential diagnosis. Both usually are polyneuropathies or mixed symmetric neuropathies rather than examples of mononeuritis multiplex. Immunopathologic neuropathy, periarteritis nodosa, collagen vasoneuropathy and Landry-Guillain-Barré polyneuritis constitute differential diagnostic problems.

Case Reports. CASE 1. A.D. This 54-year-old man was hospitalized December 15, 1957. He had had paroxysmal soreness of the throat for one month but denied infection. He stopped smoking 7 years before admission after having smoked heavily for 30 years. His chief complaint included tingling and painful paresthesia and severe lancinating root ganglionic pains of the feet, girdle areas and hands. Ascending paralysis began with foot drop and weakness of the legs. Wrist drop followed. Mild sensory deficit at this time included loss of pin point perception over the periphery of the extremities. Respiratory weakness on the 5th hospital day required mechanical respiration: Vital capacity decreased to 200 ml. Detailed neurologic examination was invalidated by respiratory weakness and irascible psychotic personality disturbance. Loss of accommodation, convergence, upward conjugate deviation, and ptosis suggested Wernicke's syndrome superimposed on polyneuropathy. The patient remained in a respirator for 30 days. On the 45th day of hospitalization he was discharged with residual weakness of the extremities more severe in the feet. During hospitalization a survey for malignancy including radiographic observation for thoracic tumor was negative. The patient remained well until 3 years later.

In December, 1960, he developed influenza and one week later noted hemoptysis. Radiographic studies, bronchoscopy, and bronchial smears substantiated a diagnosis of a large cylindroma of the right lung. Pneumonectomy was performed in January, 1961. Appropriate investigation in April, 1961, has failed to reveal metastasis or residuals of the previous polyneuropathy.

CASE 2. B.T. A man 80 years of age was admitted to the hospital on March 12, 1960, for treatment of lobar pneumonia. The chief complaint included severe root ganglionic pains in the chest, dyspnea and cyanosis of 2 days' duration. Antecedent infection was denied. Interrogation of the patient and relatives revealed that he had had occasional dysphagia and nasal regurgitation in the 2 years prior to hospitalization. Approximately one week prior to admission tingling and burning paresthesia were noted in the feet and hands. Numbness of the extremities followed. Two days later he noted weakness of the lower extremities in walking. Mild pain which began at the time of the paresthesia progressed to severe lancinating pain in the extremities and trunk. These pains were rhythmically repetitive. The patient said his feet felt "dead" and his hands "swollen." He was ataxic.

The neurologic findings included cyanosis, dyspnea, impaired intercostal and diaphragmatic movement, slurred speech, and clouded sensorium. He was unable to give the place, date, or person until oxygen and artificial respiration were administered. The tidal volume was 150 ml. and the vital capacity 600 ml. The patient had dysphagia for solids but not for saliva or fluids. Moderate interosseus atrophy of 2 years' duration was present. Ascending paralysis was progressive. In 2 days the sphincters were paralyzed and the extremities could not be moved. Lethargy, delirium and tremor varied from day to day. Retrospective falsification, ptosis, and extraocular paresis suggested Wernicke's syndrome and Korsakoff's psychosis. Areflexia developed.

Peripheral hypalgesia extended proximally to midcalf and midarm. Achilles tendon pain was decreased, graded a minus 2. Many hemorrhagic ecchymoses and ischemic lesions in the skin suggested an arteriolar-capillary dysfunction. The left lower extremity was edematous and its muscles tender to pressure. The spinal fluid protein increased from 45 to 85 mg. per 100 ml. in one week. Bronchoscopy for neoplasm was negative.

The patient succumbed to bulbar respiratory paralysis on the 20th day of hospitalization. Examination postmortem revealed a localized reticulum cell sarcoma in the left lumbosacral area. The tumor weighed 55 gm. Appropriate studies of peripheral nerve and central white matter of the nervous system failed to show any malignant cells. Atherosclerosis, generalized and coronary, was severe. The polyneuropathy of malignancy probably began 2 years prior to admission and terminated fatally prior to discovery of the neoplasm.

CASE 3. C.C. In July, 1960, a woman 41 years of age was admitted to the hospital with the chief complaint of indigestion. Subtotal gastrectomy was performed. Microscopic section revealed carcinoma *in situ*. In September, 1960, the patient was readmitted to the hospital because of repetitive lancinating pains, steady aching, and paresthesia of the feet and hands. Difficulty in walking had been increasing. These symptoms had been intermittently progressive for 3 months. Neurologic examination revealed bilateral foot drop, wrist extension weakness and sensory deficit to midthigh and midforearm. The skin of the legs was glossy and thin. The calf muscles were mildly atrophied. The Romberg was positive. The deep tendon reflexes were absent. Several necrotic areas were present in the skin of the terminal phalanges of the fingers. On funduscopic examination moderately severe atherosclerotic changes were observed. The polyneuropathy progressed in severity for one month and then subsided. The patient was discharged to her home. Four months later the polyneuropathy recurred and in one month again resolved. The patient is now well and there is no evidence of either metastatic disease or of polyneuropathy of malignancy. Radiographic study of the abdomen and thorax revealed severe atherosclerosis of the aorta.

CASE 4. C.J. A 54-year-old truck mechanic was hospitalized in December, 1956, with a diagnosis of traumatic low back syndrome. Radiographic observation of the chest showed severe atherosclerotic calcification of the arch of the aorta. Abdominal roentgenograms revealed similar calcification in the descending aorta. During the following 10 months the patient had fever, tachycardia, leukocytosis and secondary anemia. He complained of anorexia and 40 pounds weight loss. Constitutional signs such as these are not unusual in necrotizing arteriolitis and infectious immune states.

In November, 1957, pains and paresthesia occurred in all four extremities. These were sensitive to touch and pressure. The deep tendon reflexes were decreased. The right Achilles reflex was absent. Muscular paresis was present in the left biceps and deltoid, bilateral extensors of the wrists, and the dorsiflexors of the right foot and toes. Bootlet hypalgesia in the lower extremities extended proximally to midcalf. Funduscopic examination showed severe tortuosity of the venules indicative of atherosclerosis.

Ancillary studies included a negative myelogram. Skull roentgenograms were normal. Cerebrospinal fluid contained 68 mg. per 100 ml. protein and 3 cells per cm. Postural wheezing and clinical findings compatible with polyneuropathy suggested the advisability of again Roentgen-raying the chest. A large "sunburst" lesion was present in the right lung hilus. Bronchoscopy and biopsy showed inoperable squamous bronchial cancer.

The idiopathic polyneuropathy of malignancy subsided one month later and the patient was discharged. He died 6 months later at home of pneumonia. Necropsy was not performed.

CASE 5. C.A. A 55-year-old man developed what he termed an upper respiratory infection April 1, 1956. One week later he noted tingling and burning paresthesia in the periphery of the extremities especially the hands. Weakness on walking then developed. On April 23, the patient became ataxic in stance and gait. He was hospitalized at this time with a tentative diagnosis of subacute post infection polyneuropathy. During 7 weeks' hospitalization paralyses were intermittent. The face was paralyzed on each side at different times. Ataxia was intermittent. Peripheral weakness of the extremities occurred on a number of occasions. Radiographic and other observations for extraneural cancer failed to uncover any abnormality. Biopsy of muscle disclosed normal striations and fibers. Cerebrospinal fluid contained 140 mg. of protein and 150 lymphocytes per cm. The pressure was 140 mm. of water. Spinal fluid dynamics were normal. Other ancillary studies were noncontributory. In September, 1956, the polyneuropathy resolved. He remained well until January, 1957, at which time he re-

ported elsewhere for physical examination. A small node in the groin was removed for microscopic section. This showed lymphosarcoma. Mediastinal Roentgen-ray therapy for presumptive neoplasm was given. On March 18, 1957, the patient succumbed to oral hemorrhage. Necropsy demonstrated a lymphosarcoma invading the left lower lobe of the lung and the aorta. Focal collections of immature lymphocytes were found within the perineural lymphatics in the epicardium. Microscopic section disclosed disseminate lymphosarcoma of the lungs, liver, spleen, pancreas, kidneys, bone marrow, lymph nodes, and adrenals. There was grade 3 atherosclerosis of the aorta and coronary arteries.

CASE 6. B.M. A man 35 years of age was admitted to the hospital for neuritic pain in the sciatic and femoral nerve distributions of several months' duration. Recently he had also complained of lancinating pains in the neck, shoulder girdle, and arms. Neurologic examination revealed notable fasciculations in the extremities most severe in the quadriceps muscles. Severity of the fasciculations suggested motor neuron disease. There was generalized muscle weakness in the extremities. Spotty hypalgesia was present in the lower extremities. Cerebrospinal fluid dynamics and constituents were within normal range. The Queckenstedt test was negative. The pressure was 140 mm. of water. Protein was 45 mg. per 100 ml. Radiographic studies revealed an iliac lucidity which on biopsy proved to be metastatic carcinoma. Skull and spine roentgenograms failed to reveal any bony lesions, although colon contrast roentgenograms demonstrated an obstructing malignancy.

Following resection of the carcinoma the neuropathy improved but did not resolve. The patient succumbed 4 months after operation. Liver metastases and insufficiency were assumed to have caused death. Widespread metastases caused a pseudopolyneuropathy. The patient died at home and necropsy was not performed.

Scheinker[59], Kurnick and Yohalem[50], Williams, Diamond, and Craver[72], Estes and Millikan[26], Davison and Balser[20], and Crow[18] in reporting cases of multiple or single myeloma have regarded peripheral neuritis as a neuropathy of malignancy. The term myelomatous neuropathy applies to these cases. This should not be confused with metastatic compression and infiltration of nerve trunks which is referred to as pseudopolyneuropathy of multiple myeloma.

In addition to the relationship to neuropathy, malignancy may have the same or similar association with certain myopathies. The neuropathies and myopathies may occur as combined neuromyopathies of malignancy. Dermatomyositis[24,51,66,68], dermatomyositic complexes, polymyositis, scleroderma, collagen diseases, myopathies of late onset, myasthenias, and myotonias[29] likewise have occurred in association with malignancy.

Firmat and Lipsett[27] suggest that malignancy should be considered in each case of dermatomyositis. In 590 cases reviewed by Williams[72], malignancy was associated with 15%. Dermatomyositis has been reported in association with malignancy by Bezecny[5], Brunner and Lobraico[9], Christianson, Brunsting, and Perry[14], Curtis, Blaylock and Harrell[19], Grace and Dao[28], Hepp[43], Sheard and Knoepfler[61], Straus and Straus[65], and Williams[72]. Neuritic symptoms and signs were common in these cases.

Scleroderma (progressive systemic sclerosis) pathogenetically associated with premalignant or malignant changes in the lung, has been reported by Caplan[12] and Collins, Drake, and Dodge[17]. Christianson, Brunsting, and Perry[14] have reported scleroderma occurring in association with malignancy.

Pathogenetic relationships between the neuromyopathies and malignancy, as yet undefined, probably are not similar to those mechanisms interrelating pleuropulmonary cancer and the triad of hypertrophic pulmonary osteoarthropathy, Hippocratic fingers and arthralgia. It is of interest that pleuropulmonary cancer is rarely, if ever, associated with both neuropathy and pulmonary hypertrophic osteoarthropathy, although it may be associated with either alone. The significance of

this is unknown; as is the association between neural lesions and pulmonary osteoarthropathy.

Rasmussen[58] postulated a peripheral vascular mechanism in causation of hypertrophic pulmonary osteoarthropathy in one patient with bronchial cancer. He stated the lung tumor caused the vascular lesion. Hansen[33] assumed a nervous reflex in the lung produced osteoarthropathy and Hippocratic fingers in bronchial cancer patients. In one of the author's osteoarthropathy cases, hyperventilation in the right lateral recumbent position resulted in generalized cyanosis, angina, pain referred to the left mandibuloauricular area, and paroxysmal hypertension. This patient had an undiagnosed left hilar bronchial cancer. Wierman, Clagett, and McDonald[71] observed that pleural involvement in lung cancer patients appeared to be a factor in pathogenesis of pulmonary osteoarthropathy. Harper and Patterson[34] reported pulmonary osteoarthropathy may appear as long as 3 years prior to the signs of lung cancer.

Neuropathies, myopathies, and allied syndromes are associated with malignancy in similar temporal fashion. This is also true of hypertrophic pulmonary osteoarthropathy. These syndromes may occur, may run their natural course and resolve, or may be intermittent and recurring prior to and during the course of the neoplasm. Thus, definitive observation for malignancy is equally advisable in these syndromes.

Pathogenesis of idiopathic myopathies may relate especially to cancerogenesis rather than to the developed malignancy. The genesis of malignancy has defied the valiant efforts of clinician, biologist, geneticist, pathologist, bacteriologist, virologist, biochemist, immunologist, and nuclear physicist. It may be assumed on an empirical but sound basis in idiopathic neuromyopathy of malignancy there are multiple etiologic factors. Some of each are likely common to both. Many have been suggested. Zeigler and Torres[78] believe neoplasm or related metabolic factors have a noxious influence on peripheral nerve function. Clarke[15] compared carcinomatous neuropathies with war time malnutrition. Brain, Daniel and Greenfield[7] believe extrinsic poisons and intrinsic metabolic disturbances are responsible for the Purkinje cell destruction in cortical cerebellar degeneration. If this lesion runs its natural course in 2 years they postulated a 2/3 chance of association with cancer. Davison and Balsar[20] believed the neural lesions in a case of multiple myeloma were secondary to either severe anemia or unknown toxic factors. Scheinker[59] had previously suggested the latter. Denny-Brown[21] suggested primary sensory neuropathy could be a metabolic disorder related to tumor cells. The neuromuscular changes were compared to those observed in experimental pantothenic acid and vitamin E deficiency. Hart[35] suggested carcinoma cells compete for essential nutrients such as vitamins with resultant deficiency neuropathy. Joiner, McArdle, and Thompson[48] demonstrated pyruvate metabolism abnormality which in cases was correctable with intramuscular thiamin. Oestreicher, Dressler, and Middlebrook[56] have stated that isoniazid neuropathy is ameliorated by pyridoxine. This vitamin deficiency has been suggested by others as the cause of the proximal motor type of neuropathy of malignancy.

Henson, Russell, and Wilkinson[42] thought virus infection a plausible factor in causation of carcinomatous neuropathy. Dodgson and Hoffman[23] believed virus invasion of the central nervous cells should not be disregarded

as a possible etiologic factor in one case of neuropathy associated with a cancer of the esophagus. Denny-Brown[22] remarked nerve and muscle tissue are especially subject to hypersensitivity and in the development of dermatomyositis (Type I polymyositis) ischemic angiitis and antigens are important.

Grace and Dao[28] postulated dermatomyositis in malignant disease represents a sensitization reaction. Brunner and Lobraico[9] mentioned allergic reactions as eosinophilia, urticaria, erythema multiforme and erythema nodosum in dermatomyositis of malignancy. Caldwell[10] postulated the dermatomyositis complex of malignancy resulted from an hyperimmune vasculitis caused by tumor antigen. Wedgwood, Cook, and Cohen[70] related dermatomyositis to an undefined form of immune reaction. Heathfield and Williams[40] reported mononeuritis multiplex in only one of 8 cases of periarteritis nodosa. In the other 7 there was polyneuropathy. In one polyneuropathy of periarteritis nodosa a bronchial cancer was present.

The pathogenesis of neuropathy, dermatomyositis, myopathy, and allied conditions in malignancy suggests common denominators in multiple system syndromes. The basic mechanisms transcend the concept of organ specificity of disease. As an analogy, in arteriolitis, the arteriole is affected in many viscera and systems. This is of practical import, as arteriolar rupture and hemorrhage are easily observed in the skin, mucous membrane, and ocular fundus. In the deeper structures as the brain, heart, lung, and kidney similar changes may be assumed. In arteriolitis ischemic denervation of many organs and tissues produces a second multisystem disease. Likewise enzymatic and biochemical abnormality may cause a multisystem neural "breakdown." In failure of fundamental processes there may be abnormal reactions affecting immunity, reparation, regeneration, and inflammation. Metaplasia and neoplasia may eventuate.

DIFFERENTIAL DIAGNOSIS. It is of interest that clinical neurologic findings in neuropathy of malignancy rarely permit differentiation from post viral, post infection, or immune polyneuropathy of Landry-Guillain-Barré type. In neuropathy occurring simultaneously with malignancy, metastasis and infiltration must be excluded.

Multiple sclerosis, diabetes mellitus, periarteritis nodosa, dermatomyositis, scleroderma, disseminated lupus erythematosus[3,62], motor neuron disease, myasthenia gravis, myotonia, thyrotoxic myopathy, muscular dystrophy, and myxedema may be confused with idiopathic neuropathy of malignancy. Cerebellar degenerative atrophy is more often a manifestation of neuropathy of malignancy, than other processes.

Summary and Conclusions. Idiopathic neuropathy may be the first sign of cancer. Multiple unknown factors cause idiopathic neuropathy of malignancy. This syndrome is not a result of metastasis, infiltration, compression or other mechanical effects of malignancy. Disseminated malignancy may produce a pseudopolyneuropathy. The pathogenesis of neuropathy of cancer includes important mechanisms of disease production. It would appear possible that atherosclerosis, senescent arteriolar changes and autoimmune vasculitis may contribute in the pathogenesis of neuropathy of malignancy. The characters of the prevalent "vascular" neuropathies of diabetes, post infectious and hyperimmune states, and the collagen disorders are similar to that of neuropathy of cancer. In this a vascular component in pathogenesis, if present, would be one

of a number of causative mechanisms. The idiopathic neuropathy may be associated with different neoplasms in various sites. Thereby are suggested common denominators among the dissimilar neoplasms in their potential capacity to be associated with neuropathy. The interrelations between cancer and neuropathy also are present between cancer and neuromyopathies, dermatomyositis, polymyositis, arthritis, myasthenia, and myotonia. Pulmonary hypertrophic osteoarthropathy may be frequently but dissimilarly associated with pleuropulmonary cancer.

Idiopathic neuropathy and allied conditions often precede by 3 years the malignancy. Thus, pathogenetic factors may predetermine malignancy and contribute to an advanced neuropathy. In idiopathic neuropathy of malignancy one or more neural functions, tracts, or pathways may be affected. The neuropathy may occur as a single attack with resolution, may be recurrent, or progressive. Polyneuropathy is common, but not prosaic. In certain cases one or more features of a polyneuropathy may be accentuated. In post infection and autoimmune Landry-Guillain-Barré polyneuropathies, paresthesia and pain occur initially. Peripheral paralysis, often first in the foot and hand, may progress and ascend the neuraxis. Bulbar paralysis and respiratory failure should be anticipated immediately. Otherwise a serious clinical anachronism may permit anoxia of nerve cells. Sensory deficit appears, as limited or progressive paralysis becomes established. Ataxia, sensory or cerebellar, varies in prominence. The classic pain, paralytic or sensory deficit syndromes may present in miniature or caricature. These may be capricious. In many cases the clinical and morphologic findings in polyneuropathy do not differentiate the types observed in immunizations, diphtheritic and other post infectious states, drug sensitizations and the Osler-Landry-Guillain-Barré syndromes from idiopathic neuropathy associated with malignant cancer.

Clinical findings manifest during the course of polyneuropathy may resolve prior to death. Thus, in such fatal cases, the correlates of necropsy may not be translatable in clinical terms. The extent of morphologic change may not parallel the severity of clinical disease. The classic analogy is steroid-induced therapeutic paradox in periarteritis nodosa. Arteritis has been replaced by "completely healed" but occluded vital arteries in heart, brain, and kidney. The vasa nervorum also are occluded. Experience suggests an analogous situation in neuropathy of collagen and other diseases. Necropsy which does not include serial examination of peripheral nerve and arteriole sections fails to reveal significant abnormalities. Clinical phenomena which do not have morphologic basis or counterpart are not delimited by necropsy. These circumstances have a bearing on our understanding, or lack of it, of neuropathy.

In multiple system syndromes associated with malignant cancer it is fortunate that the early neuropathy is often benign. Less frequently the malignancy is low grade and the polyneuropathy is fatal. It would seem the increasing incidence of malignancy proclaims the significance of neuropathy.

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MEDICINE

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COAGULANT AND ANTICOAGULANT AGENTS IN SNAKE VENOMS

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THE snake venoms, like other secretions of the salivary glands, can be considered as mixtures of physiologically and toxicologically active substances. They may, therefore, vary quantitatively and qualitatively not only with the species of the animal but with the individual within the species as influenced by age, nutrition, climate and other environmental conditions. Most of these substances belong to the group of enzymes and cannot, therefore, be subjected easily to analytical studies.

Numerous investigators have shown that the various substances present in different snake venoms can be grouped on the basis of their various effects into the following groups:

1) Substances which act upon the blood itself or on various blood constituents. All substances belonging to this group accelerate or retard blood coagulation, cause hemolysis or diminish the motility of the leukocytes.

2) Substances which influence the circulation of the blood. Some of these act on the vasomotor center while others paralyze the peripheral blood vessels.

3) Substances which act on striated muscle by altering their permeability and producing swelling. Some also are known to produce fibrillary contractions in cardiac muscle.

4) Substances which act on smooth muscle. Their presence can best be proved on isolated organs such as the small intestine, uterus, oviduct, in which, in small doses, they produce contraction and in larger doses, paralysis.

5) Substances which influence metabolism. The venoms of *Trimeresurus macrosquamatus* and of some *Naja* species are known to be able to raise the blood sugar 200% in rabbits if administered in doses of 10 mg. per kg. of body weight. This action occurs even if the splanchnic nerves have been cut and the adrenal glands removed.

6) Various members of the genera *Bothrops, Crotalus* and *Naja* have in their venoms substances which modify the alkali reserve of the blood.

7) Cytolysins are present in various quantities in nearly all snake venoms and these quantities can easily be determined. The capacity of venoms to

eliminate histamine in the tissues is based on their cytolysin content. Consequently a sharp fall of blood pressure, brought about by the sudden liberation of histamine, is characteristic for these venoms.

8) Venoms often contain certain specific proteases which produce bleeding.

9) Recent electrophoretic studies have confirmed the existence in the venom of many species of a yolk heat-coagulation inhibitor enzyme.

10) Venoms contain several substances which especially affect the nervous system. They act on the motor nerve endings in the same manner as does curare. This effect, unlike that of curare, is not reversible and can only be set aside by the administration of a corresponding antivenin. Some of these substances only attack the sensory nerve endings without affecting the fibers themselves. Venoms, such as that of the Australian Tiger snake (*Notechis scutatus*) or of the Neotropical rattlesnake (*Crotalus terrificus*), show a special affinity for the optic nerve causing blindness even in low concentrations and in an early stage of venenation. Many venoms kill by paralyzing the respiratory center, their principal neurotoxic substance being selective for this portion of the central nervous system.

These several effects of venoms and the substances producing them[9,59,74,121] are presented in Table 1. It will be seen that at least 18 types of effect can occur.

The above list does not include certain ferments which are found generally in other animal tissues and glandular secretions, as well as venoms; for example, hyaluronidase, the spreading factor of Duran Reynals[27]. The proof of the existence of these ferments was made possible only in recent years by the application of electrophoretic or chromatographic methods in the analysis of snake venoms. Three such substances were found: two nucleotidases, one of which is capable of liberating phosphoric acid and the other decomposes the coenzyne of Warburg and hyaluronidase which dissociated hyaluronic acid. The latter ferment, according to the unconfirmed hypothesis of

Type of Active Substances in Venom	*Site of Action*
Coagulants	Blood
Anticoagulants	Blood
Hemolytic factors	Blood
Leukocytotoxins	Blood
Factors modifying alkali reserve	Blood
Vasomotor center	Circulation
Paralyzing	Blood vessels
Hemorrhagic	Blood vessels
Hyperglycemic	Metabolism
Yolk heat-coagulation inhibitor	Metabolism
Permeability altering	Striated muscles
Contracting and paralyzing	Smooth muscles
Fibrillatory	Heart muscle
Cytolysins	Tissues
Causing paralysis of sensory nerve endings	Nervous system
Causing paralysis of motor nerve endings	Nervous system
Causing paralysis of respiratory center	Nervous system
Causing action on optic nerve	Nervous system

Mann and Lutwak-Mann[95], is responsible for the rapid spread of the snake venoms in the tissues attacked.

We know relatively little of the chemical nature of the substances which bring about these effects. Until now, it has been possible to obtain in crystalline form only the lecithinase (hemolysin) of cobra venom (*Naja naja*)[22], and the neurotoxic substances from the venom of Neotropical Rattlesnake[122]. However, the latter substance has not proved to be uniform. By means of electrophoresis, introduced in 1937 by Klobusitzky and König for the separation of the different components of snake venoms, it has been possible to prove the specific nature of several components which are responsible for the 18 effects mentioned above[38,40,42,75,81,102,112].

Venom actions which have particularly interested investigators and, therefore, been most thoroughly studied are, in addition to the neurotoxic effect which causes death, those which influence blood coagulation.

Fontana, in 1767, first described snake venoms as blood coagulants and anticoagulants. This classification was maintained for several decades in spite of contradictory data published by various authors. Lacerda Filho[86] and also Brazil and Rangel Pestana[10] considered the venoms of the *Bothrops* species (formerly called *Dachesis*) to be *in vivo* anticoagulants, whereas Noc[105] reported that the venoms of these snakes accelerate blood coagulation. Sanmartino[117] confirmed that poisoning by the venom of *Bothrops alternata* (called Urutú in Brazil) diminishes the coagulability of the blood. Contrariwise, Arthus[1] reported a thrombotic effect with small doses, whereas such increased coagulability tends to diminish as larger doses are used. The venom of the puff-adder (*Bitis arietans*) was considered by Beaujean[7] to be a coagulant, whereas Link[89] believed that it had an anticoagulant effect. According to Eagle[28], the venom of the Florida diamondback (*Crotalus adamanteus*) causes coagulation, but according to Mathews[100] it has an anticoagulant action. Similarly, the venom of the Daboia viper (*Vipera Russellii,* in old terminology *Daboia elegans*) was considered by Lamb[87] and Hanut[44] to be a coagulant and by Arthus[2] and Link[89] to be an anticoagulant.

It is the purpose of this writer to discuss, on the basis of his own experimental data as well as recent data published by others, the following questions:

1) What is the reason for the above noted discrepancies?

2) Under what circumstances does a particular venom, known as a coagulant, behave as an anticoagulant?

3) Are the coagulant or anticoagulant substances identical with the neurotoxins, as maintained by Faust[29, 30] and others, or are they different substances, as maintained by Fontana[32]?

4) How do the substances which influence blood coagulation behave from the standpoint of immunology?

5) What are the possibilities of their application for therapeutic purposes, and what can be expected from such preparations?

The coagulation of the blood, in its last analysis a transformation of fibrinogen into fibrin, is a very complicated process and the details of its chemical and enzymatic reactions are not yet completely known.

It should be pointed out that in testing the effect of any substance on blood coagulation the results are largely influenced by the circumstances and conditions of the experiment. Experiments can be made with whole blood, either *in vitro* or *in vivo*, with decalcified blood, with plasma or fibrinogen solutions to which are added the substances needed for coagulation. With

snake venoms these experiments become even more complex, since in these cases the material is not a more or less well known substance, but a mixture composed wholly or in part of unknown substances which may have opposite biochemical, pharmacodynamic and enzymatic effects. Furthermore, it must be taken into consideration that relatively few of those who have written on the subject have had the opportunity of collecting the venoms personally and of making stable preparations. In the case of venoms bought in the dried state, there is always the possibility that it is a mixture of the venom of various species or that it was dried under unfavorable conditions. Experiments carried out with material that may not be wholly suitable can obviously lead to contradictory and erroneous results and conclusions.

Even with perfectly suitable venom preparations the results depend upon the conditions and circumstances of the experiments.

At first glance it seems difficult to understand these discrepancies, since it would seem to be easy to determine whether the venom has a coagulant or an anticoagulant action and one might think it sufficient to determine this action on the several factors involved in the process of coagulation and on the whole blood. Actually, however, the conditions are more complex because (a) Nearly all venoms contain both coagulant and anticoagulant substances and the effect of the venom itself, therefore, depends upon the ratio in which these exist in the sample under study; (b) If the effects are stated in relation to the several component factors in coagulation, the results are not always identical with those obtained on whole blood or "*in vivo*" because of the simultaneous presence of coagulant and anticoagulant venom constituents; (c) Many venoms contain a proteolytic ferment which can destroy fibrinogen and thus make the blood uncoagulable.

The concept that the same venom may contain both coagulant and anticoagulant substances and that the effect, therefore, will depend upon experimental conditions is rather old. Mitchell and Reichert, in 1886[103], first presented such experimental data obtained with the venom of the Florida diamondback rattlesnake, bringing this supposition into focus. In 1893, Martin[98] also noted that the venom of the same species of viper in some cases speeded up coagulation and in other instances inhibited coagulation. Later Lamb and Hanna[88] reported experiments with the venom of Daboia viper in rabbits in which the intravenous administration in a dosage of 0.075 to 0.26 mg. causes intravascular coagulation. On the other hand, when 0.5 mg. was given intravenously to two rabbits, the blood of one of them remained fluid. However, none of the above mentioned authors recognized any relation between the contradictory results and the variations in the quantity of the venom. Noc[105], in connection with the venoms of the *Bothrops* species encountered in South and Central America, was the first to state that in a low concentration these substances considerably hastened coagulation, while in higher concentrations they retarded or inhibited it.* Taylor, Mallick and Ahuja[125] as well as this author (see

*The author calls attention to the interesting fact that this double effect, varying according to the degree of concentration, is not limited to snake venoms alone. Spinal cord extracts, which accelerate coagulation, also have this property[63]. Gardikas and Kottas[35] have shown that artificially high concentrations (100 to 400% of normal) of prothrombin, Factor 5 and Factor 7 do not have an accelerating effect on coagulation but that an excess of platelets (200,000 to 1,000,000 per c.mm.) will cause a shortening of the clotting time of recalcified plasma and in the test for heparin tolerance.

Tables 1 and 4) have independently observed and published the first quantitative data on the degrees of concentration at which a given venom has the effect of accelerating coagulation and at which the same venom inhibits coagulation. Taylor and his collaborators in their experiments with rabbits and monkeys used the venom of the Daboia viper, cobra and carpet viper (also called saw-scaled viper, *Echis carinatus*) and have observed that the slowly lethal doses (1.5 mg. or more per animal) are those which inhibit coagulation. The results obtained by the author are summarized in Tables 1 to 4.

The data of the tables show quite clearly that the venoms studied by the author, if administered in a concentration lower than 0.4%, accelerate coagulation, while in a concentration of 0.4 to 4% they inhibit coagulation (higher concentrations have caused hemolysis). The author and König[76] were also able to show that snake venoms which accelerate coagulation in decalcified blood, when administered in large amounts *in vivo*, only temporarily inhibit the coagulating capacity of the

TABLE 1.—5 ML. OF NORMAL HORSE BLOOD CONTAINING 0.3% SODIUM OXALATE AND 1 ML. BOTHROPS JARARACA VENOM IN PHYSIOLOGICAL NaCl SOLUTION, ACCORDING TO KLOBUSITZKY[64]

% of venom in the mixture	.17	.08	.04	.02	.01	.005	.0025	.00125	.0006	.0003	.0001
Clotting time	does not coagulate		2′	2′	2′5″	2′5″	2′30″	3′40″	10′	12′15″	13′

TABLE 2.—UNTREATED HORSE BLOOD AND 1 ML. OF BOTHROPS JARARACA VENOM, ACCORDING TO KLOBUSITZKY[64]

Concentration of venom in blood	*Readings*	
	1 hour	*19 hours*
2.30%	Hemolysis	Hemolysis
1.39%	Liquid	Hemolysis
0.49%	Liquid	Hemolysis

TABLE 3.—NORMAL HORSE BLOOD CONTAINING 0.3% SODIUM OXALATE AND 1 ML. BOTHROPS JARARACA VENOM ACCORDING TO KLOBUSITZKY[64]

Concentration of venom in blood	*Readings*		
	1 hour	*3½ hours*	*19 hours*
6.90%	Liquid	Hemolysis	
4.16%	Liquid	Hemolysis	
1.40%	Liquid	Liquid	Hemolysis

TABLE 4.—EFFECT OF A FRACTION ISOLATED FROM THE VENOM OF BOTHROPS JARARACA BY THE METHOD OF KLOBUSITZKY AND KÖNIG[77] ON THE BLOOD COAGULATION *IN VIVO* (PIGEON), ACCORDING TO KLOBUSITZKY AND KÖNIG[76]

Concentration of the fraction (Bothropothrombin) in the blood, %	*Clotting time*		
	Before injection	*20′ after injection*	*24 hours after injection*
0.028	7′ 30″	No clot. in 24 h.	1′
0.001,4	3′ 30″	12′	3′ 30″
0.000,28	5′	3′	0′ 20″
0.000,056	5′ 30″	4′	1′
0.000,014	5′	1′	0′ 30″
0.000,005,6	5′	1′ 40″	0′ 20″

circulating blood, and that after this negative phase, which lasts about 24 hours, even these doses shorten the time of coagulation.

Similar results have been obtained by Billin[8] with the Florida diamondback rattlesnake, by the author and König[78] and Link[90] with Neotropical rattlesnake, by Césari and Boquet[16] with viper venoms (*Vipera aspis*), and by Vellard[128] with the venoms of the following snakes of Venezuela: fer-de-lance (*Bothrops atrox*), *B. nasuta*, bushmaster (*Lachesis muta*), neotropical rattlesnake and *Micrurus lemniscatus*. Many authors, mainly Europeans, working with highly diluted solutions (most probably because of lack of material) could report only coagulant effects.*

To show to what extent the results of the coagulation test depend on the method, it is sufficient to refer to the instances of the neotropical rattlesnake and the water moccasin (*Agkistrodon piscivorus*). When Link[89] first began his studies on the venom of the above mentioned *Crotalus*, he used isolated solutions of thromboplastin, prothrombin, thrombin and fibrinogen and concluded that the venom did not act as a coagulant. The author and König[78], however, observed definite coagulation, when they used normal horse blood containing 0.3% of sodium oxalate (a concentration of 0.03% of venom resulted in coagulation in 10 minutes 50 seconds). Link[90] later confirmed these results when he repeated his experiments and stated "that the method used by the previously mentioned authors is more sensitive." The venom of the water moccasin gave no coagulant effect in the *in vitro* experiments of Eagle[28], whereas Peck and Sobotka[110] found contradictory results in their *in vivo* experiments.

The venoms of the water moccasin, the Texas diamondback rattler (also called Texas rattler, *Crotalus atrox*), timber rattler or banded rattlesnake, also black rattlesnake (*Crotalus horridus*) and sand viper (*Vipera ammodytes*) decompose fibrinogen by a process of proteolysis (Eagle[28]). The venoms of *Vipera latastei* and red diamond snake (*Crotalus ruber*) act by proteolysis destroying prothrombin (Link[91]). All of these, therefore, appear to be anticoagulants; but under special conditions they can also have a coagulant effect.

Contradictory results are quite often due to the questionable origin of the venoms: mixed venoms of different species or inadequate preservation, especially in cases where the investigators work with purchased venoms.

In the light of these facts, it is not possible to classify the several species according to the coagulant capacity of their venoms. It is, however, possible to establish a sequence of diminishing coagulant capacity, as determined by the individual investigators as follows:

Bothrops jararaca>*Lachesis muta*>*Crotalus terrificus*>*Micrurus corallinus*† (Klobusitzky[64], Klobusitzky and König[79]); *Bothrops atrox*‡>*Vipera Russellii*>*Bothrops neuwiedii*>*Bothrops lanceolatus*†>*Bothrops alternata*>*Bothrops nummifer*>*Vipera aspis*>*Cerastes cornutus*>

*Cf. the papers of Hanut[44,45,46] on various species of Bothrops, on the viper, Caboia viper and horned viper (*Cerastes cornutus*).

†The former name of this genus, *Elaps*.

‡*B. atrox* and *B. lanceolatus* are the same species. This error on the part of a young author, who died a tragic death, is probably traceable to the old name, *Lachesis lanceolatus*. The venom here referred to as *B. atrox* is from Costa Rica, whereas that of *B. lanceolatus* is of Brazilian origin.

Crotalus terrificus (Hanut[46]); *Bothrops atrox*>*Cerastes cornutus*>*Vipera aspis*>*Vipera Russellii*>*Crotalus terrificus* (Césari and Boquet[17]); *Bothrops atrox*>*Lachesis muta*>*Crotalus terrificus*>*Bothrops nasuta* (Vellard[128]).

Very few experimental data have been published concerning the venoms which inhibit coagulation. Eagle[28] recently reported his experiments on this type of venom. He added various quantities of the venom under study to solutions of purified fibrin (the concentrations of venom being 0.05, 0.25, 0.0125, 0.0062, 0.0031, and 0.0015%) and after the fibrinogen had remained unchanged for 30 minutes he added the same quantity of thrombin solution to the test samples and then observed the time necessary for the fibrinogen to be converted into fibrin. On the basis of his results the following sequence of decreasing inhibitive effects on coagulation can be stated:

Vipera ammodytes>*Agkistrodon piscivorus*>*Crotalus terrificus*>*Crotalus atrox*>*Bitis arietans*>*Merremia haemachates*>mixed venoms of different species of *Micrurus*>*Vipera Russellii*>*Naja naja*>*Naja flava*>*Notechis scutatus.*

On comparing the sequences of venoms which cause coagulation with those which inhibit it, it is remarkable that even Eagle puts the *Notechis scutatus* first in the one and then also in the other sequence. This contradiction may also be due to variations in the conditions of the experiments. It should be noted that the venom of this snake is unable to convert purified fibrinogen into fibrin, but since it can transform prothrombin into thrombin when tested in whole blood, it will show an accelerating effect upon coagulation.*

Contradictory observations have also been published as previously mentioned with regard to the venom of daboia viper. Therefore, Devi, Bose and Sarkar[25] have recently reinvestigated this problem and have found that this venom has a marked clot-promoting property which is caused by a substance with a prothrombin-like action. The clotting power of this venom has also been verified in 6 patients with a Factor VII deficiency. The application of daboia viper venom in dilutions of 1:10,000 or 1:20,000 removed the clotting defect in 4 patients (Hougie, Barrow and Graham[53])†

In regard to the matter of acceleration of coagulation, aside from the fact that large doses introduced *in vivo* temporarily inhibit coagulation, it should be noted that some venoms also affect decalcified blood while others only affect whole blood. Furthermore, in regard to the venoms which affect decalcified blood, attention should be called to the fact that they are able to accelerate *in vivo* the coagulation of the blood in patients with hemophilia and certain other hemorrhagic disorders (Peck, Crimmins and Erf[107], Klobusitzky[65], Crambock[20], Boquet[9]).

In addition to the above mentioned species, various authors (Kellaway[61], Mednikyan[101], Brazil and Rangel Pestana[11], Link[89], Klobusitzky and König[78], Césari and Boquet[17]) have found that the venoms of the following snakes have inhibitive effects on coagulation:

*Riesser and Nagel[114] and also Cotti and Larizza[19] have proved that pectins, hydrochloric acid and other inorganic acids, which under normal circumstances assist coagulation of calcium-containing blood, cause an inhibition of coagulation under exceptional circumstances.

†Certainly Zürn[130] goes too far when he suggests that the coagulant factor of this venom could be very effective in the treatment of hemophilias A and B.

Death adder (*Acanthopis antarcticus*), *Agkistrodon blomhoffii*, *Bungarus fasciatus*, *Crotalus ruber*, Australian copperhead (*Denisonia superba*), *Micrurus frontalis*, Cleopatra cobra (*Naja haie*), spitting cobra (*Merremia haemachates*, old name: *Sepedon haemachates*) and Bosnian viper (*Vipera mesocoronis*, also called *V. bosniensis*).

Snake venoms belonging to the group which can accelerate the coagulation of whole blood only, produce these effects by converting prothrombin into thrombin (Eagle[28], Porges[113], Gengou[36]).

With regard to the details of the thrombin effect as well as of the activation of prothrombin, the opinions of various authors are divergent. The generally advocated view of recent authors accords to the substance which accelerates coagulation a proteolytic effect. However, this must be considered doubtful in the case of the venom of *Bothrops jararaca*. Henriques *et al.*[50] have isolated by electrophoresis its coagulating factor from one of the proteolytic ferments (protease A) which exists in this venom. The clotting substance thus purified did not show "the common properties of a proteolytic enzyme." Therefore, it cannot be stated at this time whether there is also a causal relation between the two effects, since the purified anticoagulants of other venoms have not yet been examined for their proteolytic capacity.

The coagulation-accelerating factor, affecting both whole blood and decalcified blood, was for the first time obtained from the venom of *Bothrops jararaca* by this author and König[77] but only in the form of a fairly pure aqueous solution. Later, Rosenfeld and Rubinstein[116] also succeeded in isolating from the venom of the tiger snake a substance with similar effect by means of a careful precipitation with hydrochloric acid, also in the form of an aqueous solution.

The substance obtained from the venom of *Bothrops jararaca*, called "Haemocoagulase" by the above mentioned authors, differs from the natural venom in the following ways:

a) It has no anticoagulant effect even in very high concentration (0.06%).

b) It reduces by one-half the shortest time of coagulation obtainable with natural venom.

c) Its toxic effect is about 1/11 to 1/12 of that of the natural venom.

The fraction isolated from the venom of the tiger snake proved to have a much greater coagulant effect than the initial substance and its toxicity was 1500 times less.

The chemical composition of both of these substances is as yet unknown because the quantities available are too small to be analyzed, but they are probably ferments (Boquet[9], Kaiser and Michl[59], Klobusitzky[63], Slotta[121]).

The fact that these substances are ferments can be established not only on the basis of their adsorption, thermolability, colloidal character, and sensitivity to so-called ferment toxins, but also from the fact that the temperatures at which the coagulant agents are inactivated differ from those at which the neurotoxins are inactivated. Thus the neurotoxin of *Bothrops atrox* of Costa Rica becomes inactivated at 65° C. and that of *Bothrops jararacussu* of Brazil at 110° C., while the coagulant capacities of these venoms are destroyed at 80° C. and 85° C. respectively (Klobusitzky[66]).

The immunological behavior of the coagulant factors have been studied by a number of investigators. Table 5 compiles the results of these studies.

The data of this table reveal two interesting facts with regard to the antivenins of *Crotalus terrificus* and *Bitis arietans*. In the former, in spite

TABLE 5.—NEUTRALIZING POWER OF VARIOUS ANTIVENINS IN RELATION TO THE NEUROTOXIC AND COAGULANT CONSTITUENTS

Antivenin obtained by immunization with	*Neutralizing power against the constituent (+ = effective, − = ineffective)*	*Authors*
Venom of *Crotalus terrificus*	− "H" of *Bothrops jararaca* − C of " " + N of " "	
Venom of *Lachesis muta*	+ "H" of *B. jararaca* + C of " "	Klobusitzky and König[78]
Venoms of *Micrurus corallinus* and *M. frontalis*	− "H" of *B. jararaca* − C of " "	
"H"	− C of *C. terrificus* + "H" of *B. jararaca*	Klobusitzky and König[80]
Antivenin obtained in the Inst. for Infect. Dis., Tokyo without indicating the resp. snakes (*Agkistrodon blomhoffi*[2]	− C of *C. terrificus* − C of *B. jararaca* − C of *B. atrox* + C of *B. flavoviridis*	
Venom of *C. terrificus*	− N of *B. atrox* − N of *B. flavoviridis*	Vellard[129]
Venom of *Vipera aspis*	− C of *C. terrificus* − C of *B. jararaca* − C of *B. atrox* − C of *B. flavoviridis*	
Venoms of *Bitis arietans* and *Sepedon haemachates*	+ C of Cerastes cornutus + C of V. aspis + C of V. Russellii − N of " " − N of *C. terrificus* − N of *B. atrox* + N of *V. lebetina*	César and Boquet[17]
Venom of *V. aspis*	+ C of *Cerastes cornutus* + C of *V. lebetina*	
Venom of *C. cornutus*	+ C of *V. aspis*	César and Boquet[18]
Venom of *Naja naja*	+ C of *V. lebetina*	
Venom of *V. Russellii*	− C of *Echis carinatus*	Taylor, Mallick and Ahuja[125]
Venom of *C. carinatus*	− C of *V. Russellii*	

Abbreviations: C = Coagulant effect; "H" Haemocoagulase (Bothropothrombin); N = Neurotoxic effect.

of the fact that the antivenin neutralizes the neurotoxic effect of the venom of *Bothrops jararaca,* it does not neutralize either the coagulant effect of the same venom or of the coagulant substance isolated from that venom. In the latter, the antivenin behaves in just the opposite manner, for it neutralizes the coagulant effect but not the neurotoxic action of the venom of the *Vipera Russellii.* The snakes belonging to the genera *Bothrops* and *Crotalus* are of the same family (*Familia Crotalidae*) and the genera of *Bitis* and *Vipera* belong to the same subfamily of the *Viperinae.*

In the author's opinion these facts are important from a general biological point of view, since they imply that the chemical structure of the neurotoxins and that of the other components occurring in the natural venom are independent of the zoological classification, or more correctly, they are not necessarily related to the zoological class into which the serpents in question have been placed. Of course, it would be erroneous to conclude from this that the presently accepted classification of venomous snakes is incorrect by assuming this fact to be incompatible with such classification. This is certainly not the case. It must simply be acknowledged that environment and circumstances of living exert so strong and intense an effect on these animals that their venomous secretions, although probably originally identical, have undergone more or less profound modifications. The previously mentioned investigations of Vellard[129] clearly prove that the Venezuelian snakes are quite different from the same speciments of Central and South America.

As to the antigenic nature of the isolated coagulant substance, there is to the author's knowledge only one supporting fact, and none at all as to that of the anticoagulant substance. Klobusitzky and König[80] immunized two goats with "Haemocoagulase" and found that the serum thus obtained had a much lower potency with regard to its coagulant capacity than did the antivenin obtained by the use of natural venom. They, therefore, attribute a haptene nature to the coagulant substance.

The anticoagulant effect of those venoms which have only this effect might be considered as having arisen by two different mechanisms which, in contrast to the process of acceleration of coagulation, can be developed in parallel, as if one were dealing with a primary and a secondary effect. Most probably the primary effect consists in an enzymatic separation of thromboplastin. This factor is only slightly sensitive to heat and, in addition, is neutralized in most cases by the specific antivenin. Thus the anticoagulant component of the venom of Cobra if kept below 75° C. for 45 minutes becomes inactive (Kruse and Dam[84]). In the case of several other venoms such as those of the water moccasin, Texas rattler, timber rattler, puff-adder (Eagle[28]) and the red rattler (*Crotalus ruber*) (Link[89]), it could be claimed that they contain a specific protease which rapidly dissolves the fibrin.

Up to now there is no irrefutable explanation for the inhibition of coagulation brought about by large doses of a venom which normally expedites coagulation. The most probable explanation is that these venoms also contain a small amount of a ferment that splits thromboplastin and which is soon exhausted or inactivated by the circulating blood, thus enabling the component which accelerates coagulation to exert its effects. The previously mentioned fact, that the substances which speed up coagulation do not in a purified state cause inhibition of coagulation, is sufficient proof for the dual nature of these components.

The immunological behavior of the

anticoagulant factor has thus far been investigated only by Césari and Boquet[17]. They have found that the bivalent antivenin, obtained by immunization with the venoms of *Bitis arietans* and *Sepedon haemachates* neutralizes the anticoagulant capacity of the venoms of *Naja naja* and *Naja flava*.

During the past decade there have been published the results of many studies by various authors on the mechanism of action of "haemocoagulase," that is, of the coagulating ferment of the venom of *Bothrops jararaca*. These authors have approached these problems from different points of view. Several have made experiments *in vivo*, while others have used blood, plasma, or fibrinogen as their test materials. In the experiments performed *in vivo* it has been found that:

a) The ferment distinctly hastens blood coagulation even in a concentration as low as 5×10^{-8}[76].

b) Its coagulant effect appears in the rabbit on subcutaneous administration after 15 minutes and less than 21 minutes; on intramuscular administration after 10 minutes and less than 16 minutes; while on intravenous administration after 3 minutes and within 7 minutes[69].

c) One-seventieth part per kilogram of body weight of that quantity, which produces firm clotting within 9 to 10 minutes at 20 to 22° C. in 5 ml. of decalcified blood, reduces the time of coagulation in the rabbit for 96 hours and in the human being for 2 to 3 days[31].

d) The quantity mentioned in (c) diminishes by 1/2 to 1/3 the clotting time in rabbits[69].

e) The ferment, even in large quantities, never causes thrombosis or embolism.

f) There exists an antagonism between the effect of the ferment and that of heparin. Seven thousand I.U. of heparin neutralizes with safety the effect of that amount of ferment which produces a firm clot in decalcified blood under the conditions mentioned above in (c)[70].

g) 2-Phenyl-1-2-Inandion and dicoumarin do not neutralize the coagulant effect of the ferment[73].

h) The quantity of ferment mentioned above in (c) neutralizes two hundred times more hirudin *in vivo* than *in vitro*[73].* This marked discrepancy between its *in vivo* and its *in vitro* effect has particular significance, since Markwardt[97] showed that the neutralization of plasma by hirudin is a true chemical reaction.

The chief purpose of the experiments performed *in vivo* was to establish in which phase of coagulation this ferment acts, and to determine whether the substances which take part in the normal coagulation process, acting as activators or inhibitors, influence the coagulant effect of the ferment, and if so, how.

This group of experiments could be considered to be a logical continuation of those initiated in 1767 by Fontana[32] using the natural venoms of snakes and continued without interruption by many other investigators.

With regard to the purified ferment, aside from its previously mentioned ability to cause coagulation of even decalcified blood, the following facts have been established:

a) This ferment is more sensitive to heat than is its corresponding natural venom. The ferment loses its activity when heated to 80° C. for 5 minutes, while this temperature does not alter the coagulant ability of natural venom[16,54,64].

b) The coagulation times resulting from the use of the ferment are the

* Hirudin of high purity, prepared by Markwardt[96], was used.

same in both decalcified blood and plasma[71].

c) The ferment shortens recalcification time[21].

d) The ferment is less sensitive to heat and to an acid medium than is thrombin[55].

e) The ferment acts on the coagulation of plasma, regardless of the presence or number of platelets[71].

Deutsch[23] by his studies added these verified observations:

f) The coagulant power of the ferment is not modified by the action on convertin.

g) The ferment increases the effect of protamine sulphate on the fibrinogen in the absence of thrombin.

h) The ferment diminishes the effect of hirudin on the fibrinogen.

i) Substances with an antithrombin effect have only a very limited influence on this ferment.

It must be mentioned that, although the corresponding experiments were carried out with the natural venom of *Bothrops atrox*, the fibrin formed by the coagulant effect of that venom is soluble in urea when calcium and a thermolabile factor are present, in contrast to fibrin clots formed by thrombin coagulation which are insoluble[56]. Furthermore, the coagulating power of natural snake venoms, including that of the *Bothrops* snakes, is inactivated by specific antithrombin[28,113].

In view of these results, there should be no doubt that this ferment contains within itself the properties of thromboplastin and of thrombin. On the other hand, among the findings above listed there exist some which prove that this ferment is not identical with the thrombin formed in plasma by the complicated catalytic process commonly referred to as the first phase of coagulation. Therefore, it must be considered to be a thrombin complex *sui generis* to which might be applied the name bothropothrombin[72]. This view of ours has been generally accepted (Deutsch[24], Hohnen[51], Koller[82], Stacher and Bohnel-Zehetmayr[123]).

The fact that this ferment acts on decalcified blood is explained by its "thrombin" nature, and its accelerating effect on normal blood could be explained by the supposition that it is more active than is blood thrombin. This supposition is based on the experiments previously mentioned which showed that the antithrombin substances act more weakly on this ferment than they do on blood thrombin.

This quality of the ferment is responsible for the fact that it does not influence the so-called second phase of coagulation, that is, the transformation of fibrinogen into fibrin.

As to the manner of its action, one cannot yet formulate a definite opinion, because of certain details that have not yet been clarified. Some of these remaining doubts probably derive from the incomplete purity of the ferment preparations. It is quite possible that the solutions thus far obtained may be a mixture of two substances, one being of thromboplastin nature and the other with thrombin properties. If such be the case, the proportion of these two substances and the quantity present in the blood or plasma of factors which inhibit or favor the transformation of thromboplastin into thrombin can considerably influence the results.

With regard to the well established coagulant effect of the venoms of more than a dozen species of snakes, it would indeed be astonishing if this quality had not been applied for therapeutic purposes. And so indeed it has. Long ago when our views concerning the mechanism of the coagulant action of these venoms and the nature of the coagulant substances were still incomplete, two North American physicians,

Peck[106] and Frank[33], experimented with highly diluted venom of water moccasin (Cottonmouth) in the treatment of menorrhagia. They started on the basis of observations on rats by Peck and Sobotka[110] to the effect that these animals did not react with the Shwartzman phenomenon when they were injected with small doses (0.1 mg.) of this snake venom. On the basis of the favorable results of Peck and Frank, additional North American and European physicians began clinical experimentation in the treatment of hemorrhagic disorders of the most varied nature by using water moccasin (*Agkistrodon piscivourus*) venom as well as the venoms of *Vipera Russellii*, *Notechis scutatus*, *Cerastes cornutus*, *Naja naja*, *Bothrops atrox* and *B. jararaca* (Baker and Gibson[4], Hance[43], Jargreaves[47], Koressios[83], Macfarlane and Barnett[93], Peck, Crimmins and Erf[107], Peck and Goldberger[108], Peck and Rosenthal[109], Rosenfeld and Lenke[115], and Sergent[120]. The Council of Pharmacy and Chemistry, on the basis of the good results obtained by North American observers, have expressed as long as 15 years ago a favorable opinion on the therapeutic value of the snake venoms with clotting properties[57,58].

In order to be able to put on the market easily controllable preparations with predictable uniform effects, the Preparation Board of the Brazilian Academy of Pharmacy for the First Panamerican Pharmaceutic Congress, held in December, 1948, in Havana, Cuba, honored this author by requesting him to report on this subject and to prepare recommendations of standards for pharmaceutical preparations of this type to be submitted to the above mentioned Congress. The author's recommendations had reference chiefly to the following qualifications:

1) To establish an easily determinable coagulant unit for animal test.*

2) The establishment of criteria for the nontoxic nature of the preparations.

3) The setting of a time limit within which the preparations will maintain their potency.

4) Procedures to eliminate proteins (because of their allergic effect[67]).

In addition to the earlier and almost exclusively North American publications, notably Brazilian authors have written about the clinical application of purified venoms in speeding up coagulation and about the results obtained (Azevedo[3], Barbosa[5], Buchert[15], Freire[34], Klobusitzky[68], Moacyr[104], Vaz and Pereira[127], and others). In addition, there are publications about results obtained in Europe and later in America (Breda, Bernardi and Sala[12], Grundmann[41], Kauer, Bird and Reznikoff[60], Kleinmann, Page and Preisler[62], Macht[92], Malmierca[94], Mauro[99], Schmidt[119], Stöger[124], Valejo Botas[126], and others).

In recent years various European clinics have experimented with purified ferment in prophylactic preoperative medication to reduce blood loss as well as in the treatment of hemorrhage from various causes.†

With regard to its use as a prophylactic or a therapeutic measure in persons with nonpathological blood coagulation and who do not present any extensive destructive lesions in the tissues, the results are to be classified

*The clotting unit proposed was the smallest quantity of the coagulant substance which, dissolved in 1 ml. of physiological saline solution causes firm clotting within 8 to 10 minutes at 20 to 22° C. in 5 ml. of 0.3% sodium oxalate in horse blood.

†An Austrian product called "Reptilase," prepared by the firm Disperga in Vienna was employed; 1 ml. Reptilase diminishes by 1/2 to 1/3 the clotting time in adults with a physiological clotting mechanism for from 36 to 60 hours.

as favorable. To date, 1,373 adequately controlled clinical cases have been recorded with the following distribution and results (Table 6)..†

The clinical application of this ferment in cases of pathologically altered coagulation must be based on its particular qualities and the role which may be attributed to it in the coagulation process. The ferment is considered as a thrombin: therefore, it could be expected favorably to influence coagulation in hemorrhagic disorders, which are caused by prothrombin deficiency, deficiency of the accelerators in the transformation of prothrombin into thrombin or deficiency of Factor V or Factor VII.‡ It is not to be expected that the ferment should cause the blood to coagulate in cases of essential hemophilia, fibrinogenopenia or afibrinogenemia. There is no doubt, however, that in certain cases of prolonged clotting time (12 to 20 minutes) the ferment can correct the abnormality.

The number of well classified hemorrhagic disorders thus far treated, particularly because of the relative rarity of these diseases, is quite small and the results thus far published are contradictory.* Therefore, the only conclusion to be drawn for the present is that the ferment does not cure any hemorrhagic diseases; its favorable effect, if there be one, is transitory and symptomatic.

Among the contraindications mentioned in the reports of the various observers, the outstanding one is that which refers to the influence of the ferment on the number of platelets. Cravarezza and Stura[21] found that the ferment causes a reduction in the num-

TABLE 6.—DISTRIBUTION AND RESULTS OF CLINICAL CASES TREATED BY ISOLATED COAGULANT FERMENT (REPTILASE)

	No. of cases treated	*No. of satisfactory results*	*% of satisfactory results*
Various plastics procedures[13]	357	357	100
Plastic procedures according to Thiersch[13]	241	241	100
Gynecology and Obstetrics[6,21,48,49]	215	207	96
General and Emergency Surgery[13,14]	150	150	100
Oto-Rhino-Laryngology[37,39,111]	125	120	96
Outpatients Surgery[13]	116	116	100
Urology (principally Prostatectomies)[85]	64	53	83
Odontology, Jaw Surgery[26]	50	50	100
Phthisiology[118]	45	45	100
Medicine[123]	10	10	100
Total	1.373	1,349 (aver.)	98.3

†The number of reported favorable cases exceeds 5,000.

‡It must here again be mentioned that Hougie, Barrow and Graham[53] have experimented with Russel viper venom in dilutions of 1:10,000 and 1:20,000 in 6 cases of proconvertin deficiency. They obtained a favorable effect in 4 cases.

*Holzknecht[52] recently published one case of serious postoperative bleeding in a patient with hemophilia A who did not react to treatment with antihemophilic globulin; however, after the application of Reptilase combined with transfusion of fresh blood, the bleeding stopped. The ineffectiveness of the coagulation ferment in the treatment of hemophilia A has also been confirmd by Dix[26]. This author reported 3 cases of this disease in which Reptilase alone was unable to stop the bleeding.

ber of platelets and that this reduction is the more marked when additional ferment is used. On the other hand, Glaninger[37] and Heiss[48,49] state that the ferment does not influence the number of platelets. Experiments by the author, carried out in horse plasma that had been subjected to low and high velocity centrifugation, did not demonstrate any effect of the platelets on the coagulation induced by the ferment[71]. In view of the fact that the platelets play a preponderant role in coagulation, the application of the ferment in hemorrhagic disorders definitely requires clarification of the effect of this ferment on human platelets.

There is no possibility for the therapeutic application of those snake venoms with anticoagulant effects until the anticoagulant component can be adequately separated from the toxin. The preparation of these two constituents, at least in the case of the venoms thus far examined, is so unfavorable that the application of dilute solutions is impossible. Furthermore, solutions that have been diluted to the degree that they can be safely administered no longer have an adequate anticoagulant effect.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

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Contrast Between the Growth of Embryonic Chick and Rat Bones Cultivated on a Natural and a Chemically Defined Medium. J. D. BIGGERS, PH.D., R. B. L. GWATKIN, PH.D. AND SUSAN HEYNER, PH.D. (The Wistar Institute, Philadelphia, Pennsylvania.). The cartilaginous tibiotarsii from 7-day-old chick embryos and 17-day-old rat embryos have been cultivated on either a homologous natural medium, or a chemically defined medium (BGJ). The natural media were prepared from either heparinized chick or rat plasma and chick or rat embryo extract. The chemically defined medium is a relatively simple one which we have recently designed. Its composition is shown in Table 1. The bones were cultivated with the floating lens paper technique (Chen, 1954), in an atmosphere of humidified 5% carbon dioxide in air. In other work it has been shown that the responses of chick and rat bones are very dependent on the concentration of glucose in the medium (Biggers, Rinaldini and Webb, 1957; Heyner and Biggers, 1958). Sufficient glucose has therefore been added to the media to prevent glucose starvation.

The growth of both chick and rat bones has been measured in terms of length, wet weight and dry weight. In addition the increase in deoxyribonucleic acid (DNA) in chick bones has been measured, using the indole color reaction.

In both species the embryonic bones elongated more on medium BGJ than

TABLE 1.—CHEMICALLY DEFINED MEDIUM BGJ

	mg./100 ml.	*mM*		*mg./100 ml.*		*mg./100 ml.*
L-lysine hydrochloride	24	1.31	nicotinamide	2.0	calcium lactate	55.5
L-histidine hydrochloride H_2O	15	0.72	thiamine hydrochloride	0.4	potassium chloride	53.0
L-arginine hydrochloride	7.5	0.36	calcium pantothenate	0.02	potassium dihydrogen phosphate	16.0
L-threonine	7.5	0.63	riboflavin	0.02	sodium chloride	800.0
L-valine	6.5	0.56	pyridoxal phosphate	0.02	magnesium sulphate ($7H_2O$)	20.0
L-leucine	5.0	0.38	folic acid	0.02	sodium bicarbonate	350.0
L-isoleucine	3.0	0.23	biotin	0.02		
L-methionine	5.0	0.34	*p*-aminobenzoic acid	0.2		
L-phenylalanine	5.0	0.30	α-tocopherol phosphate (sodium salt)	0.1		
L-tryptophan	4.0	0.20				
L-tyrosine	4.0	0.22	choline chloride	5.0	glucose	500.0
L-cysteine hydrochloride H_2O	9.0	0.51	*m*-inositol	0.02	phenol red	2.0
			vitamin B_{12}	0.004	streptomycin	5.0
					penicillin	10,000 units
L-glutamine	20.0	1.37				

on the natural media. Conversely, the wet and dry weights increased more in the bones cultivated on the natural media. Throughout the period of cultivation there was a tendency for the dry weight/wet weight ratio to fall. This was particularly so in the rat bones cultivated on medium BGJ.

In the chick the DNA content of the bones increased comparably on both media for the first 6 days *in vitro*. Thereafter the DNA increased in the bones cultivated on the natural medium but not in those cultivated on medium BGJ.

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Heyner, S., and **Biggers, J. D.:** Nature, **182**, 810, 1958.

Inhibitory Effect of Acetylcholine on Glycogenolysis in the Heart. SYDNEY ELLIS, PH.D., AND NORMA H. VINCENT, PH.D. (Department of Pharmacology, Woman's Medical College of Pennsylvania, Philadelphia). In isolated perfused guinea pig hearts acetylcholine inhibited the glycogenolytic effect as well as the chronotropic and inotropic effects of epinephrine. When the heart rate was controlled by electrical stimulation, acetylcholine, without modifying the rate, inhibited epinephrine glycogenolysis. Atropine antagonized all the inhibitory actions of acetylcholine. Epinephrine produced positive inotropic and glycogenolytic effects, but no chronotropic effect, in the presence of veratramine. Dichloroisoproterenol inhibited all three effects of epinephrine. Acetylcholine also inhibited glycogenolysis induced by theophylline. Acetylcholine produced a partial, but significant, inhibition of anoxic glycogenolysis in the atria, but not in the ventricles. On the basis of the above results a metabolic role for acetylcholine in the control of cardiac glycogen catabolism is proposed. These findings also suggest a possible biochemical basis underlying the physiological control of cardiac function by acetylcholine.

Effect of Thyroid Powder or Propyl Thiouracil on the Composition of Liver and Plasma Lipids of the Chick. J. D. EVANS, PH.D., N. L. OLEKSYSHYN, P. J. MIDDLETON, AND H. G. SCHWARTZ, PH.D. (Department of Physiology, Temple University Medical School). Chicks receiving a synthetic diet containing 0.5% cholesterol and 10% corn oil were further supplemented with thyroid powder or thiouracil at 2 different dosage levels. After 7 to 21 days, plasma and liver lipids were extracted and fractionated into principal lipid components by silicic acid chromatography. The fatty acids of each component were recovered and analyzed by ultra violet spectrophotometry. Desiccated thyroid reduced liver sterol esters to 28% of control values, with only small reductions in the other liver lipid components. Thyroid did not alter greatly the distribution of fatty acids in liver sterol esters and therefore cholesteryl monoenoate which constituted 70% of fatty acids was the principal compound removed. All plasma lipid components were decreased after thyroid powder and increased after thiouracil, but the characteristic distribution of fatty acids in each fraction was not greatly changed. However, minor but consistent distributional differences in the fatty acids of phospholipids suggested that thyroid facilitates the transformation of dienoic to tetraenoic acid. Thiouracil opposes this reaction. From

the fact that the thyroid principle counteracts the specific accumulation of liver cholesteryl monoeonate following dietary cholesterol supplementation in chicks, we conclude that thyroid regulates in part by facilitating both cholesterol and oleic acid metabolism.

The Effect of Ionizing Irradiation on the Lipids of the Liver Mitochondria of Rats. H. P. Schwarz, L. Dreisbach, M. Barrionuevo, A. Kleschick, and I. Kostyk (Division of Biochemistry of Philadelphia General Hospital, Philadelphia, Pennsylvania). Female rats weighing 200 gm. were irradiated to the whole body at 1000 r, then kept fasting and sacrificed 24 hr. after the exposure to Roentgen-rays. The lipids of freeze dried liver mitochondria of the irradiated rats and controls were examined. Total lipids and total fatty acids were significantly increased by the irradiation, while cholesterol, cholesteryl esters, total lipid phosphorus, alkali stable phosphorus, phosphatidyl ethanolamine, and phosphatidyl serine remained unchanged and phosphatidyl choline even showed a significant decrease after irradiation. This finding was further clarified by the detection of a substantially elevated bis-phosphatidic acid fraction in the irradiated mitochondria. The bis-phosphatidic acid fraction was isolated by chromatography on silicic acid columns, showed a fatty acid: phosphorus ratio of almost 4:1, and paper chromatograms and infrared spectra quite similar to those of a synthetic bis-phosphatidic acid. Gas chromatography of the fatty acid esters prepared from this fraction showed that the bis-phosphatidic acid fraction did not contain a single compound, but comprised a number of compounds of different fatty acid composition. This work was carried out under Contract AT(30-1) 1864 with the U.S. Atomic Energy Commission.

BOOK REVIEWS AND NOTICES

INSIDE THE LIVING CELL. By J. A. V. BUTLER, D.Sc., F.R.S. Pp. 174; 18 ills. New York: Basic Books, Inc., 1959. Price, $3.50.

THIS is a most lucid, interpretative discourse on the implications of a number of recent research findings with regard to "the living cell."

Dr. Butler opens his book with a description of living cells and their constituents. Then there follows a systematic discussion of: How the Cell Lives, Vitamins and Antivitamins, Cell Division, Inside the Cell, Genes and Mutations, Effects of Radiations on Living Cells, Viruses as Cell Parasites, A Community of Cells, Chemical Messengers, Antibodies and Immunity, Cancer, Origin of Life and Photosynthesis, Specialized Cells: Muscles, Nerves and Sense Organs, The Brain, Actions and How They are Performed, Using Tools and Symbols, Is the Brain a Calculating Machine?, Aging and Death, and Life in the Universe.

The author, an eminent biophysicist and chemist, shows a remarkable grasp of the wide spectrum of topics noted above. Moreover, he combines this with a highly readable style. This book will be interesting, informative and stimulating to "students of science and also to scientists who are not experts."

C.Z.

FUNDAMENTALS OF CLINICAL HEMATOLOGY. By BYRD S. LEAVELL, M.D., Professor of Internal Medicine, and OSCAR A. THORUP, JR., M.D., Associate Professor of Internal Medicine, University of Virginia School of Medicine. Pp. 503; illustrated. Philadelphia: W. B. Saunders Co., 1960. Price, $10.00.

THIS is a simply written textbook of hematology. The subject matter includes the origin, morphology, chemistry and function of blood cells; hemoglobin and iron metabolism; mechanisms of anemia; clinical syndromes associated with anemia; polycythemia; blood coagulation; disorders of hemostasis; leukocytes; leukemia; agents used in the treatment of leukemias and lymphomas; multiple myeloma; and hematologic techniques.

The authors have generally succeeded in their effort to produce a volume restricted to the needs of the practicing physician and medical student. It cannot be recommended to more advanced workers in the field.

C.Z.

CONGENITAL MALFORMATIONS (Ciba Foundation Symposium). Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch. AND CECELIA M. O'CONNOR, B.Sc. Pp. 308; 91 ills. Boston: Little, Brown & Company, 1960. Price, $9.00.

THIS report of a Ciba Foundation Symposium devoted to Congenital Malformations contains 12 papers concerning various aspects of the subject and the general discussion of each. The participants, who were clinicians, veterinarians and basic scientists, are all currently studying some aspect of the problem and are experts in their particular fields.

The main concentration was upon the genetic and chromosomal causes of abnormal development and the teratogenic effects of drugs, chemicals and certain nutritional defects. Most of the papers and the discussions concern the experimental production of various anomalies and are of greater interest to those studying the problem than to clinicians. Several of the papers, however, particularly those devoted to chromosomal abnormalities, anencephaly, hydramnios and the role of prediabetes and diabetes have more clinical implications.

While it is evident that much more work is necessary for a complete understanding of the methods by which fetal abnormalities occur the progress during recent years is remarkable.

J.W.

DAS MENSCHLICHE KNOCHENMARK. By PROF. DR. KARL ROHR. 3rd ed. Pp. 593; 244 ills. Stuttgart: Georg Thieme Verlag, 1960 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $23.35.

THIS is the latest edition of an excellent German treatise on the human bone-marrow. There is a systematic discussion of methods for obtaining marrow specimens for study, the embryology of bone-marrow elements, and of the morphologic features of the marrow constituents. This is followed by a careful and comprehensive consideration of the changes induced in marrow components by various disease states with, of course, principal emphasis on the primary blood dyscrasias.

The text is thoroughly illustrated and the color plates are of excellent quality. Hematologists and pathologists who read German will find this a worthwhile reference text. C.Z.

INFECTIOUS DISEASES OF CHILDREN. By SAUL KRUGMAN AND ROBERT WARD, New York University and University of Southern California. 2nd ed. Pp. 398; 55 ills. St. Louis: C. V. Mosby Co., 1960. Price, $13.00.

THIS second edition, like the first, presents its information in a succinct straightforward style lending to facile readability. Numerous lists, tables and diagrams complement the text nicely. The newer infectious viral agents, an appraisal of poliomyelitis and rabies vaccine, and related matters bring the volume up-to-date. The treatment of bacterial meningitides is well presented and the much disputed use of adrenal steroids in these infections is evaluated reasonably. References at the end of each chapter are representative, accurate and current. Those physicians in need of a handbook of easy reference on the subject may find their investment in this volume worthwhile. A.B.

THE PLASMA PROTEINS. VOL. 2. BIOSYNTHESIS, METABOLISM, ALTERATIONS IN DISEASE. Edited by FRANK W. PUTNAM, Department of Biochemistry, University of Florida. Pp. 518; illustrated. New York and London: Academic Press, Inc., 1960. Price, $14.00.

THE second volume of this contemporary treatise places emphasis on the physiological role and metabolic interrelationships of plasma proteins in health and in disease. Topics considered in this volume include the following: Structure and Function of Human Serum Lipoproteins, Plasma Enzymes, Circulating Hormones, Blood Coagulation, Comparative Biochemistry and Embryology, Biosynthesis of Plasma Proteins, Alterations of Plasma Protein Patterns in Disease, Abnormal Serum Globulins, and Genetic Alterations in the Plasma Proteins of Man.

The chapters are all written by outstanding authorities. This book and its companion volume are highly recommended to anyone wishing a comprehensive reference which deals with the plasma protein system as a whole. C.Z.

FALLOUT: A STUDY OF SUPERBOMBS, STRONTIUM 90, AND SURVIVAL. Edited by JOHN M. FOWLER. Pp. 235; 33 ills. New York: Basic Books, Inc., 1960. Price, $5.50.

THIS book undertakes the presentation of a balanced and understandable account of nuclear weapons and the multitude of hazards they have created for mankind. The Foreword is written by Adlai E. Stevenson, who early appreciated the important implications for society of nuclear weapons and their testing. A number of prominent scientists authored the succeeding chapters in which consideration is given to The Bombs and Their Products, The Global Pattern of Fallout, From Bomb to Man, The Rising Level of Fallout, Biological Effects of Radiation, Radiation and Future Generations, Radiation Accidents, Protection and Treatment, Detection of Bomb Tests, Nuclear War, and National Survival. The Honorable Representative, Chet Holifield, has written a careful appraisal of the Civil Defense situation in the United States.

There are also instructive appendices on The Fundamentals of Radiation and Fission and Fusion, as well as a list of all 203 announced nuclear explosions up to late 1958.

Lucidly and authoritatively written, and, concerned as it is with a subject of vital national and global significance, this book is highly recommended to all responsible citizens. C.Z.

ERGEBNISSE DER BLUTTRANSFUSIONSFORSCHUNG, VOL. 5. Edited by DR. H. BAUMANN. Pp. 257; 66 ills. Basel and New York: S. Karger, 1960 (Albert J. Phiebig, Box 352, White Plains, N.Y., U.S. Agent). Price, $10.00.

THIS volume contains the proceedings of the meeting of the German Society for Blood Transfusion which was held in Salzburg in 1959. The papers and the discussions are in German and will be of particular interest to those workers who are concerned with the collection, storage, grouping, matching, and clinical use of blood and blood substitutes. C.Z.

LA PHYSIOLOGIE DES SINUS: SES APPLICATIONS CLINIQUES ET THERAPEUTIQUES. By L. FLOTTES, P. CLERC, R. RIU AND F. DEVILLA, with the assistance of R. GUILLERM, R. BADRÉ AND R. LE DON. Pp. 592; 253 ills. Paris: Librairie Arnette, 1960. Price, NF. 75.

THIS unique monograph introduces a number of important innovations including emphasis on physiologic processes and extensive correlation of basic science with the subject matter. The first section considers anatomy, embryology, histology and comparative anatomy, the second section is devoted to the physiology of the sinus structures and the final section deals with clinical considerations. Valuable information is afforded on vascular and lymphatic dysfunction, the dynamics of sinus ventilation, the role of the ostia and

controversial measures such as aerosol therapy. Constant emphasis on the importance of therapeutic conservatism in dealing with mucous membrane structures and on the restoration of physiologic function is a refreshing feature of this work. The numerous illustrations are of the highest quality and an excellent bibliography follows each subject. Rhinologists will find this monograph indispensable. H.S.

MINERAL METABOLISM: AN ADVANCED TREATISE. VOLUME 1, PART A: PRINCIPLES, PROCESSES AND SYSTEMS. Edited by C. F. COMAR AND FELIX BRONNER. Pp. 416; illustrated. New York: Academic Press, Inc., 1960. Price, $12.00.

THIS is the first volume of an advanced treatise on mineral metabolism. The respective chapters are contributed by authorities who are actively engaged in the area discussed. Topics dealt with include: Homeostasis in Mineral Metabolism; Thermodynamic Principles and Concepts; Cybernetic Aspects of Homeostasis; Chelation; Compartmental Methods of Kinetic Analysis; Ion Transport; Body Fluid Dynamics; Intestinal Absorption and Excretion; Renal Excretory Mechanisms; and Extrarenal Regulation with Special Reference to the Sweat Glands.

Research workers in biology and medicine will find this a valuable reference text on the role of minerals in physiologic, biochemical, and nutritional phenomena. C.Z.

DEMONSTRATION OF PHYSICAL SIGNS IN CLINICAL SURGERY. By HAMILTON BAILEY, F.R.C.S. (ENG.), F.A.C.S., F.R.S.E., Emeritus Surgeon, Royal Northern Hospital, London. 13th ed. Pp. 928; 1084 ills. Baltimore: The Williams & Wilkins Co., 1960. Price, $14.50.

DR. BAILEY says in his preface to this, the thirteenth edition of his magnificent text, "I believe that the majority of clinical teachers would testify that careful methods of physical examination have, at the present time, become not less, but even more, important." To this the reviewer says, "Amen," and again, "Amen." It is most unfortunate that younger physicians appear to be relying more and more on machine-made diagnoses. They have become "end-of-the-bed and viewbox physicians." There has ensued, as night follows day, an atrophy of physical diagnostic ability, and it is no wonder they learn not to depend on the results of their occasional, cursory excursions into bedside examination. It is to be hoped that a book such as this one will be discovered and used constantly by those physicians who honestly want to acquire some of the diagnostic acumen of the great examiners of yesteryear. It is an excellent volume, not only for the surgeon, but for the internist as well since it is required of him to be, among many other things, a first class general diagnostician. For the general practitioner and medical student it is also an unexcelled book for study and reference. It is fortunate that Dr. Bailey has seen fit to expand greatly the amount of material as compared with the already quite large previous editions, and he has continued the plan of presentations in the form of a series of demonstrations, profusely illustrated. The book should enjoy even greater popularity than previously.

T.D.

THE CENTRAL NERVOUS SYSTEM AND BEHAVIOR. Edited by MARY A. B. BRAZIER, D.Sc., Neurophysiological Laboratory, Massachusetts General Hospital. Pp. 475; 201 ills. New York: The Josiah Macy, Jr. Foundation and The National Science Foundation, 1960. Price, $7.50.

THIS volume contains the transactions of the third conference on The Central Nervous System and Behavior which was held in February, 1960, under the auspices of the Josiah Macy, Jr. Foundation and the National Science Foundation. The major topics considered at this meeting were: The Evolution of Man's Brain; Biochemical Maturation of the Central Nervous System; Neuronal Models and the Orienting Reflex; Concepts of Drive; Affectional Behavior in the Infant Monkey; Verbal Regulation of Behavior; and Signaling Systems in the Development of Cognitive Functions.

In addition, there is appended a list of pertinent articles which have been translated from the Russian medical literature.

Investigators in relevant areas will find this a valuable reference volume. C.Z.

PRINCIPLES OF HUMAN GENETICS. By CURT STERN, University of California, Berkeley. 2nd ed. Pp. 753; 265 ills. San Francisco: W. H. Freeman and Co., 1960. Price, $9.50.

THE first edition of this well-known textbook on human genetics appeared more than a decade ago. Tremendous strides have been made in the interim so that the publication

of the present edition is indeed timely. As before, major emphasis is placed on principles, but there is also enough detail to satisfy the needs of the great majority of students and physicians for information in this area.

The Biological Basis of Man's Inheritance, Genic Action, Meiosis, Simple Single Factor Inheritance, Lethal and Sublethal Genes, Genetic Counseling, Medicolegal Applications, Linkage and Crossing Over, Prenatal Interactions, Consanguinity, Mutations, Genetic Hazards of Radiation, Heredity and Environment, Selection, and The Origin of Human Diversity are among the subjects considered.

The volume is well-illustrated and there is an adequate bibliography. In addition, a number of problems are presented at the end of each chapter which further enhances its teaching potential. This book is recommended not only as a textbook for students, but also as a reference text for scholars in other fields who are seeking a background in human genetics. C.Z.

LE FOIE ALCOOLIQUE DE L'HÉPATITE A LA CIRRHOSE ALCOOLIQUE. By P. ETIENNE-MARTIN, Professor of Medicine, University of Lyon, and CL. KLEPPING, Assistant in Medicine, University of Dijon. Pp. 157; 7 ills. Paris: Masson et Cie, 1960. Price, 20 NF.

Though this monograph contains a review of the entire subject of alcoholic cirrhosis of the liver, American readers will no doubt be most interested in the epidemiologic information that it contains, plus the details of the approach taken by the French government to control alcoholism. During the German occupation of France the consumption of alcohol and the mortality from cirrhosis were at a very low level, but since the war, and until 1957, there was a progressive and alarming increase in both. Though the people of France represent only 2% of the world population, they consume a third of the total wine production. A very considerable percentage of Frenchmen drink as much as 2 to 4 liters a day! Presumably consequent upon high alcohol consumption, mortality from cirrhosis rose from 7 per 100,000 in 1946, at the end of the occupation period, to 33 per 100,000 in 1956. Fortunately, a reversal of the trend was noted in 1957, with a further decline in 1958, presumably the result of the governmental anti-alcoholism campaign. The present French slogan is: "Santé-Sobriété." Let us hope that Americans have the good sense to profit by the experience of others! T.D.

A SYSTEM OF MEDICAL HYPNOSIS. By AINSLIE MEARES, M.D., President, International Society for Clinical and Experimental Hypnosis. Pp. 484. Philadelphia and London: W. B. Saunders Co., 1960. Price, $10.00.

THE author lucidly describes medical hypnosis as he personally does it and he offers the reasons for his practices. The scope of the book is evidenced by the titles of its five main sections: I. The Nature of Hypnosis; II. The Induction of Hypnosis; III. Suggestive Therapy; IV. Hypnoanalysis; V. Hypnosis in General Medicine.

This book contains a wealth of practical information which will interest the inexperienced hypnotist. It offers an excellent orientation to hypnosis for the psychiatrist interested in the subject. M.B.

THE ADHESIVENESS OF HUMAN BLOOD PLATELETS IN VITRO. By ARVID JOHN HELLEM, M.D. Pp. 132; 22 ills. Boston, Oslo, London: Oslo University Press, 1960. Price, $2.40.

IN this book, the author reports the results of some ingenious and painstaking investigations on platelet adhesiveness. Sections are devoted, in turn, to methods of assay of platelet adhesiveness; platelet adhesiveness in healthy persons; the influence of red blood cells on platelet adhesiveness; and to this property of platelets in bleeding disorders.

Hematologists, especially those concerned with coagulation mechanisms, will find much new and interesting information in this monograph. C.Z.

L'ANNEE ENDOCRINOLOGIQUE. By M. ALBEAUX-FERNET, L. BELLOT, P. BUGARD, L. CANET, J. CHABOT, J. DERIBREAUX, M. GELINET AND J. D. ROMANI. Pp. 210; 12 ills. Paris: Masson et Cie, 1960. Price, 24 NF.

THIS volume, written by a group of leading French endocrinologists, is the twelfth annual review of the literature dealing with the endocrine glands. It is very much like similar volumes produced in this country, but has the advantage of fresh viewpoints and good summarization of work by outstanding French investigators, such as J. D. Romani. The chapter on the pituitary adrenal system makes particularly valuable reading. Other

chapters deal with pheochromocytomas, non-neoplastic hirsutism, the catabolic functions of the adrenal cortex, radioactive iodine uptake, adult primary myxedema, thyroiditis and autoantibodies, the thyroid effects of tri-iodo-thyronine and of sex hormones, human somatotropin, non-neoplastic hypophyseal nanism, the syndromes of Chiari-Frommel and Argonz-Del Castillo, hypophysectomy (radioactive and surgical), intersexuality, tests of ovulation, the remaining ovary after unilateral oophorectomy, oral antidiabetic agents, hormone therapy of chronic arthritis, and the histologic basis and the techniques of treatment of the Waterhouse-Friderichsen syndrome. There is an excellent bibliography which includes a good selection of world literature. T.D.

Regulation of the Inorganic Ion Content of Cells. Ciba Foundation Study Group No. 5. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. Pp. 100; 16 ills. Boston: Little, Brown & Co., 1960.

This small volume contains the proceedings of a one-day conference by the Ciba Foundation Study Group No. 5 which met in April, 1960, to discuss the Regulation of Inorganic Ion Content of Cells. Energy barriers to active transport in muscle; osmotic regulation and ion transport of frog skin epithelium; changes in passive cation permeability of erythrocytes in low electrolyte media; and the effect of complete and partial inhibition of metabolism on active transport in nerve and muscle are among the subjects discussed.

Physiologists, biochemists, and others working on ion transport mechanisms will find this an interesting and informative book. C.Z.

Lipide Metabolism. Edited by Konrad Bloch, Department of Chemistry, Harvard University. Pp. 411; illustrated. New York: John Wiley & Sons, 1960. Price, $10.50.

This volume, planned as a companion to Hanahan's "Lipide Chemistry," is a series of contributions which deal with the transformations of living systems and by isolated enzymes. Topics covered include Enzymatic Mechanisms of Fatty Acid Oxidation and Synthesis; Mechanisms of Fatty Acid Oxidation and Synthesis; Metabolism of Unsaturated Fatty Acids, Phosphatides, and Glycerides; Lipolytic Enzymes; Hormonal Regulation of Fatty Acid Metabolism; Formation and Metabolism of Bile Acids; and Chemistry and Metabolism of Bacterial Lipides.

Biochemists and others desiring contemporary discussions of the foregoing areas of lipid metabolism will find this an excellent reference. C.Z.

Dietary Proteins in Health and Disease. By James B. Allison, Ph.D., Director and William H. Fitzpatrick, Ph.D., Honorary Associate Research Specialist, Bureau of Biological Research, Rutgers University. Pp. 86; 12 ills. Springfield, Ill.: Charles C Thomas, 1960. Price, $4.50.

The chemical dynamics of various structural protein units are discussed in this volume of the series of publications on "Living Chemistry." There is a concise review of such basic concepts as the indispensable requirement for amino acids, amino acid transport, protein synthesis, catabolism vs. anabolism, labile protein reserves, protein malnutrition, resistance to disease, and specific amino acid deficiencies. Then follows a consideration of digestion, nitrogen balance, proteins and growth, calories and proteins, plasma and liver proteins, and other interrelated aspects of proteins in nutrition.

While the discussions are primarily biochemical in orientation, both clinical investigators and clinical practitioners will find much in this monograph that is pertinent to their interests. C.Z.

Blood Diseases of Infancy and Childhood. By Carl H. Smith, M.A., M.D., Professor of Clinical Pediatrics, Cornell University Medical College. Pp. 572; 51 ills. St. Louis: C. V. Mosby Co., 1960. Price, $17.00.

This is an excellent textbook of pediatric hematology. Chapters are devoted to the conventional areas of red blood cells and associated disorders, leukocytes, leukemias, and so on. In addition, there are chapters on the Origin and Development of Blood Cells, Blood Changes During Growth, Blood Dyscrasias in Relation to Maternal-Fetal Interaction, Transfusions in Pediatric Practice, The Differential Diagnosis of Jaundice in the Neonatal Period, Erythroblastosis Fetalis, Hereditary Hemoglobinopathies, Disorders of the Spleen and the Reticuloendothelial System, Blood Coagulation, and the Purpuras.

The text is well illustrated, and the references are adequate for the most part. It may be recommended to medical students and practicing physicians. C.Z.

QUANTITATIVE CELLULAR HAEMATOLOGY. By J. M. YOFFEY, D.Sc., M.D., F.R.C.S.(ENG.), Professor of Anatomy, University of Bristol, Bristol, England. Pp. 122; 17 ills. Springfield, Ill.: Charles C Thomas, 1960. Price, $5.50.

IN this excellent monograph, the author summarizes the main trends in a series of original hematological studies which he and his associates have conducted over a number of years. Discussed in turn are the Lymphoid Complex; Lymphocyte Production and Its Measurement; Lymphocyte Regulation; Lymphoid Tissue and Antibody Formation; The Quantitative Study of Bone Marrow; The Granular Cells of the Marrow—The Myeloid Equation; The Erythroid Equation; The Lymphocyte in Bone Marrow; and The Role of the Lymphocyte in Haemopoiesis.

The volume is lucidly written and well illustrated. Hematologists and others interested in the dynamics of blood cell formation will find this book to be both informative and stimulating. C.Z.

DISEASE, LIFE AND MAN. SELECTED ESSAYS BY RUDOLF VIRCHOW. Translated and with an Introduction by LELLAND J. RATHER. Pp. 273. Stanford, Calif.: Stanford University Press, 1958. Price, $5.00.

FEW men have exerted a greater influence on the course of medicine than did Rudolf Virchow. Some insight as to his role in this connection can be gained by reading 10 selected essays written by him over a period dating from 1847 to 1898. Included in this collection are two essays on "Standpoints in Scientific Medicine" (1847 and 1877), as well as his widely known "Cellular Pathology."

The value of this book is further enhanced by an interpretive introduction by Dr. Rather who also made the English translations. This is enjoyable and informative reading for pathologists and others interested in the history of medicine. C.Z.

THE HUMAN BLOOD PROTEINS. BY PROF. FERDINAND WUHRMANN, M.D., AND CHARLIE WUNDERLY, PH.D. Translated from the Third and Completely Revised Edition by HARVEY T. ADELSON, M.D. Pp. 491; 179 ills. New York: Grune & Stratton, Inc., 1960. Price, $15.75.

THIS is the English translation of the 3rd edition of an outstanding text which deals with the methods of examination and the clinical and practical significance of the human plasma proteins.

The subject matter is divided into the following major sections: 1) Chemistry of the Plasma Proteins; 2) Reactions of Proteins; 3) Methods of Examination; 4) Clinical-Chemical Methods; 5) Clinical Significance of the Plasma Proteins; 6) Clinical Significance of Dysproteinemia and 7) The Formation and Synthesis of the Blood Proteins.

The text is very well illustrated including a number of excellent plates in color. There is a comprehensive bibliography up to 1956 and a few 1957 titles. By and large, this is a superb compilation of the pertinent information up to the time of original publication. It is highly recommended as a basic reference source on the laboratory and clinical aspects of plasma proteins. C.Z.

PROTEIN AND AMINO ACID NUTRITION. Edited by ANTHONY A. ALBANESE, St. Luke's Convalescent Hospital, Greenwich, Conn. Pp. 604; illustrated. New York: Academic Press, Inc., 1959. Price, $16.00.

IT is the purpose of this volume to present rather detailed discussions of the currently available knowledge concerned with the protein and amino acid requirements in nutrition. As Dr. Albanese states so well, "The unprecedented research activity in this field and in related areas during the past decade has resulted in a gradually increasing limitation of space in the periodical literature which can be allotted to review, reflections, and speculations on the broad significance of experimental findings. These publication restrictions tend to retard the continuity of scientific thought and progress. One solution to the problem appears to be the use of media which can provide qualified investigators ample space and freedom to express themselves fully in the area of their major cognizance."

Dr. Albanese and an outstanding group of contributors are to be commended for the fulfillment of their aims to present a contemporary assessment of information dealing with this area of nutrition. Biochemists, biologists, nutritionists, clinical investigators, and clinicians will find this a valuable reference work. C.Z

SYLLABUS OF LABORATORY EXAMINATIONS IN CLINICAL DIAGNOSIS. Edited by LOT B. PAGE, M.D., Chief of Hypertension Clinic,

Massachusetts General Hospital, and PERRY J. CULVER, M.D., Associate Physician, Massachusetts General Hospital. Revised edition. Pp. 580. Cambridge: Harvard University Press, 1960. Price, $12.50.

THIS volume is a revised, up-to-date version and successor to the original Syllabus which was edited by Thomas Hale Ham and is noted for its high standard of excellence. The present edition has maintained Ham's general format and standards. It consists of a systematic discussion of the laboratory procedures that are conventionally included in texts of this type, including tests of the blood and bone-marrow elements, urine, sputum, plasma and extracellular fluids, and so forth. In addition, there are clear and concise chapters on tests concerned with the hemorrhagic disorders; renal function; gastric function; the liver and biliary system; carbohydrate metabolism; thyroid function; ovarian and testicular function; adrenal function; calcium, phosphorus, and bone metabolism; cardiac catheterization; and pulmonary function.

All who deal with the clinical application of laboratory tests will find this an invaluable guide in their selection and proper use.

C.Z.

REPRODUCTIVE PHYSIOLOGY. BY A. V. NALBANDOV, University of Illinois. Pp. 271; 38 ills. San Francisco and London: W. H. Freeman and Company, 1958. Price, $6.75.

THIS book was prepared to supplement a series of lectures on reproductive physiology given to students in fields which varied from Zoology and Veterinary Medicine to home economics and is not intended to be an encyclopedic test. Despite this it is remarkably complete and presents not only a general survey of the available information concerning reproduction in various species of birds and animals but a considerable amount of interesting and detailed material on certain specific phases of the process.

Sex and sex determination is reviewed briefly as is reproductive embryology and endocrinology. Specific problems of reproduction, such as sterility and fertility, production and transportation of spermatozoa and ova, fertilization and implantation are reviewed in more detail and direct comparisons are made between various species. Naturally much of the material concerns non-human species, but as the author points out, the basic process is the same and much of what is learned from the study of animals can be applied to the human being.

Medical students, residents and practicing physicians, as well as investigators, can learn much from this book and anyone who studies it can acquire a good bit of information about reproduction which is not only useful but of great general interest. How many obstetricians or even endocrinologists, for instance, know that in most birds only the left ovary is functional and that if it is removed soon after hatching the rudimentary right ovary will develop into a functioning testes, but if the left ovary is removed later the rudimentary one will become a proper ovary?

J.W.

THE SURGICAL TREATMENT OF PORTAL HYPERTENSION, BLEEDING ESOPHAGEAL VARICES AND ASCITES. BY M. JUDSON MACKBY, M.D., Staff Surgeon, Kaiser Foundation, San Francisco, California. Pp. 250; 49 ills. Springfield, Ill.: Charles C Thomas, 1960. Price, $10.50.

THIS book is a well organized monograph outlining the anatomy, pathophysiology and diagnosis of bleeding esophageal varices and ascites as well as the authors personal approach to the problem and management. In addition to this, there is an extensive bibliography that is quite up-to-date and there is a brief expression of opinion from other surgeons interested in the field as canvassed by the author. The book is particularly useful to the young surgeon and resident as there is considerable space devoted to technique. The monograph also presents a challenge in that many of the poorly understood features concerning portal hypertension and its effects are rather clearly outlined by the author.

R.T.

SYMPOSIUM BIOLOGICA HUNGARICA. I. HYPOTHALAMUS-HYPOPHYSENSYSTEM UND NEUROSEKRETION. Symposium in Tihany, June, 1958. Edited by I. TÖRÖ AND M. MÜLLER, Institute for Histology, Medical School University of Budapest, Hungary. Pp. 207; illustrated. Budapest: Hungarian Academy of Sciences, 1960. Price, $5.00.

THIS volume represents the first of a series of symposia organized by the biology section of the Hungarian Academy of Sciences. The contributors are members of German, Hungarian, Yugoslavian, Russian and Czechoslovakian institutions; however, the articles are published in German and French. They give a vivid picture of the enormous development that has taken place in the study of neurosecretion since Scherrer's discovery in 1928.

The relationship of neurosecretion to the hypothalamo-hypophyseal system of mammals under various conditions of stress is the chief topic. Final chapters deal with the neurosecretion in avertebrates. The book will be of interest not only to biologists but also to clinicians dealing with endocrine problems.

E.S.

HUMAN NUTRITION HISTORIC AND SCIENTIFIC. Edited by IAGO GALDSTON, M.D. The New York Academy of Medicine. Pp. 321;16 ills. New York: International Universities Press, Inc., 1960. Price, $6.00.

IN the foreword it is asserted that the knowledge acquired during recent decades has raised our concepts of nutrition from the slough of empiricism to a fairly precise science. This point of view seems hardly to describe the development of the science of nutrition which has been noted since its inception for careful, painstaking research and remarkable discoveries. The thrilling story of these investigations is recounted by the venerable Dr. McCollum in a chapter entitled "From Hopkins to the Present." An equally interesting historic episode is that of the "Development of Improved Crops" by Henry A. Wallace. This volume serves well to orient the reader into the problems of nutrition viewed in a comprehensive perspective of world-wide scope and interest. It is highly recommended.

C.S.

HAEMOPOIESIS: CELL PRODUCTION AND ITS REGULATION. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P., and MAEVE O'CONNOR, B.A. Pp. 490; 107 ills. Boston: Little, Brown & Co., 1960. Price, $11.00.

THE sixtieth symposium to be sponsored by the Ciba Foundation was devoted to the most recent findings in the field of hemopoiesis. The presentations were oriented to a consideration of cell production and its regulation. Much new information has accrued in this field in recent years and a number of investigators who contributed to this progress participated in the symposium. Among the topics dealt with are: "The lymphomyeloid complex" by J. M. Yoffey; "The use of tritiated thymidine in the study of haemopoietic cell proliferation" by E. P. Cronkite *et al.*; "Differentiation, proliferation and maturation of haemopoietic cells studied in tissue culture," by G. Astaldi; "On the destination of thymus lymphocytes," by K. E. Fichtelius; and "Factors in the control of haemopoiesis" by J. W. Linman and F. H. Bethell.

Hematologists and other workers investigating factors concerned with cell maturation and proliferation will find much valuable information in the recorded proceedings of this symposium.

C.Z.

YEAR BOOK OF GENERAL SURGERY, 1960-1961. Edited by MICHAEL E. DEBAKEY, M.D., Head of the Department of Surgery, Baylor University College of Medicine with a section on Anesthesia edited by STUART C. CULLEN, M.D., Professor and Chairman, Department of Anesthesia, University of California Medical Center, San Francisco. Pp. 593; 184 ills. Chicago: Year Book Publishers, Inc., 1960. Price, $8.00.

THE current Year Book of Surgery upholds the general excellence of the Year Book series which generally manages to include something about the more significant areas of interest to the surgeon that have occurred over the past year. This year book represents no changes from previous years and is in reality a collection of papers that have been presented in the surgical literature over the past year with editorial comments. The editorial comments are usually quite succinct and appropriate.

R.T.

LE TRAITEMENT DE LA PARALYSIE FACIALE APRES FRACTURE DU ROCHER. By G. F. GREINER, G. KLOTZ AND J. GAILLARD with the collaboration of F. ISCH. A report at the 1960 Congress of the French Society of Otorhinolaryngology. Pp. 182; 43 ills. Paris: Librairie Arnette, 1960. Price, paper back. 25 NF.

THIS small paper back monograph, written in French, presents the views of the authors on the surgical treatment of facial paralysis secondary to a fracture and injury of the facial nerve in the petrous bone. They state that the present progress in microsurgery of the ear has placed the otologist in a favorable position to treat such lesions.

Their monograph is divided into the following chapters: 1) Historical aspects, 2) Review of Anatomy, 3) The mechanism and pathogenesis of lesions of the facial nerve, 4) The histological and physiologic pathology of lesions of this nerve, 5) Indications for operations, 6) Electrodiagnosis, 7) Techniques of surgery, 8) Observations and clinical records of the operations, 9) Opinions

by other authorities in this field, 10) Conclusions.

An extensive bibliography concludes the monograph.

This book will be of interest to the otologist as well as the neurologist and neurosurgeon. It would have a wider circulation in this country if translated into English.

M.S.

LE FONCTIONS DE NIDATION UTERINE ET LEURS TROUBLES. National Society for the Study of Sterility and Fertility, Paris, France. Pp. 390; 82 ills. Paris: Masson et Cie, 1960. Price, 60 NF.

THE entire session of the National Society for the Study of Sterility and Fertility reported here was devoted to implantation of the fertilized ovum in the uterus in the human being as well as in experimental animals. After opening papers concerning the mechanism of implantation in various species of animals specific aspects of the problem were discussed in detail. The subjects which were considered included the physiologic mechanisms of implantation in rabbits, monkeys and man. A review of local biochemical and histochemical changes associated with the normal endometrial phases and with nidation, secretory activity of the decidual associated with implantation, changes in vascularity and activity of the uterine muscle and some factors related to early abortion.

Each author is an authority on the subject upon which he reports and most of the papers contain broad reviews of the material as well as the specific contributions of the authors. The investigations consist of photographs, photomicrographs and drawings all of which are clearly reproduced.

This volume should be of particular value to investigators working in the general field of reproduction but it also contains a considerable amount of information which might prove valuable to clinicians. J.W.

Handbook of Circulation, Analysis and Compilation. BY PHILIP J. ALTMAN, prepared under the direction of the Committee on the Handbook of Biological Data, Division of Biology and Agriculture, The National Academy of Sciences, The National Research Council. Pp. 365; 135 tables. Philadelphia and London: W. B. Saunders Co., 1959. Price, $7.50.

THE Handbook is a valuable source of authoritative information. It brings together data in a form that makes them much more easily available and hence useful. The contributors are all among the leaders in their field. Each section is well prepared. The data have been critically reviewed and authenticated. This book should be a prime source for all those concerned with the circulation. M.O.

Deuterium Isotope Effects in Chemistry and Biology. BY DAVID KRITCHEVSKY AND JOSEPH J. KATZ AND 36 OTHERS. Pp. 208; illustrated. New York: New York Academy of Sciences, 1960.

Biochemistry and Pharmacology of Compounds Derived From Marine Organisms. BY ROSS F. NIGRELLI AND 62 OTHERS. Pp. 335; illustrated. New York: New York Academy of Sciences, 1960. Price, $5.00.

Slice Reconstructions of Human Cerebral Sections. BY W. J. S. KRIEG, PH.D., Professor of Anatomy, Northwestern University Medical School. Pp. 27; 16 ills. Evanston, Ill.: Brain Books, 1960. Price, $1.00.

THIS series of frontal sections through the cerebral hemispheres is a supplement to the 3rd edition of the author's well known functional Neuroanatomy. Sections, selected from a series of 3,000 slides, are reproduced on the right hand pages and corresponding three-dimensional reconstructions of cortex and principal internal cerebral structures are depicted on the left hand pages. A close study of these drawings will be repaid with a fuller understanding of cerebral anatomy than is possible to obtain anywhere else today. E.S.

Clinical Physiology, Volume 1. BY K. E. ROBERTS, U.S.P.H.S. Hospital, San Francisco, California. Pp. 208; 62 ills. San Francisco: The Filmer Brothers Press, 1960. Price, $6.50.

THIS deals with water and electrolyte metabolism, kidney and gastrointestinal function, and with hepatic failure. The presentation is simplified but very pleasing and well done. In each case the fundamental physiological principles concerned are stressed. The book is intended for students and new physicians. It can be highly recommended for those who wish to make a proper beginning by basing their diagnoses and treatment on a knowledge of fundamental physiology. M.O.

Laboratory Manual of Medical Microbiology. BY JANET B. GUNNISON, Associate Professor of Microbiology, University of California School of Medicine. Pp. 252. Palo Alto, Calif.: N-P Publications, 1960. Price, $3.50.

THE author states that this paperbound 5½ x 8½" manual is a laboratory guide for medical, dental, dental hygiene, and pharmacy students. It does not include detailed instructions of procedures which are to be supplied by the individual instructors. This manual is not likely to fit the needs of many instructors except those who want a laboratory text to support discussions in diagnostic and hospital (disinfection, milk and water analysis, sterility testing) microbiology. E.S.

Culture, Society, and Health. By DOROTHY L. KEUR AND VERA RUBIN AND 40 OTHERS. (Ann. New York Acad. Sci., Vol. 84, Art. 17). Pp. 277; illustrated. New York: New York Academy of Sciences, 1960.

Fundamentals of Psychology: The Psychology of Thinking. (Ann. New York Acad. Sci., Vol. 91, Art. 1). By J. P. GUILFORD, J. S. BRUNER, C. N. COFER, K. GOLDSTEIN, E. HARMS, D. M. JOHNSON, T. S. KENDLER, A. S. LUCHINS, D. W. TAYLOR, W. E. VINACKE AND L. WELCH. Pp. 158; illustrated. New York: New York Academy of Sciences, 1960.

Textbook of Medical Physiology. By ARTHUR C. GUYTON, M.D., University of Mississippi School of Medicine, 2nd ed. Pp. 1154; 774 ills. Philadelphia: W. B. Saunders Co., 1961. Price, $15.50.

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Human Decisions in Complex Systems. By WARREN S. MCCULLOCH AND 19 OTHERS. (Ann. New York Acad. Sci., Vol. 89, Art. 5). Pp. 181; illustrated. New York: New York Academy of Sciences, 1961.

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